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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C07D 337/08, A61K 31/38, A61P 35/00, 31/18	A1	(11) International Publication Number: <b>WO 00/37455</b> (43) International Publication Date: 29 June 2000 (29.06.00)
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(21) International Application Number: PCT/JP99/07148

(22) International Filing Date: 20 December 1999 (20.12.99)

(30) Priority Data:  
10/363404 21 December 1998 (21.12.98) JP  
11/170212 16 June 1999 (16.06.99) JP

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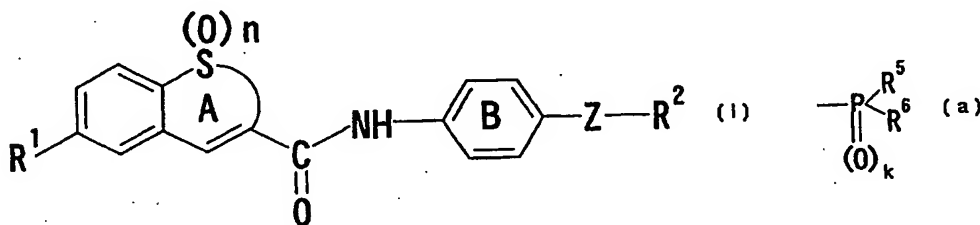
(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR,  
BY, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID,  
IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA,  
MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI,  
SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA,  
ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ,  
UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD,  
RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK,  
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI  
patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR,  
NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the  
claims and to be republished in the event of the receipt of  
amendments.

(54) Title: BENZOTHIOPIN-ANILIDE DERIVATIVES, THEIR PRODUCTION AND THEIR USE FOR ANTAGONIZING CCR-5



(57) Abstract

This invention is to provide compound of formula (I) wherein R<sup>1</sup> is an optionally substituted 5- to 6-membered ring; the ring A is an optionally substituted 6- to 7-membered ring; the ring B is an optionally substituted benzene ring; n is an integer of 1 or 2; Z is a chemical bond or a divalent group; R<sup>2</sup> is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of formula (a); wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof, which is useful for antagonizing CCR5 and also for the prevention and treatment of infectious disease of HIV.

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## DESCRIPTION

BENZOTHIOPIN-ANILIDE DERIVATIVES, THEIR PRODUCTION AND THEIR USE FOR ANTAGONIZING CCR-5

5    Technical Field

        The present invention relates to a novel anilide derivative, production and use thereof.

        Background Art

10          Recently, HIV (human immunodeficiency virus) protease inhibitors are developed for method of the treatment of AIDS (acquired immunological deficient syndrome) and use of the protease inhibitors in combination with conventional two HIV reverse transcriptase inhibitors provides with a  
15    further progress of the treatment of AIDS. However, these drugs and their combination use are not sufficient for the eradication of AIDS, and development of new anti-AIDS drugs having different activity and mechanism are sought for.

        As a receptor from which HIV invades to a target cell,  
20    CD4 is so far known, and recently CCR5 as a second receptor of macrophage-tropic HIV and CXCR4 as a second receptor of T cell-tropic HIV, each of which is G protein-coupled chemokine receptor having seven transmembrane domains, are respectively found out. These chemokine receptors are  
25    thought to play an essential role in establishment and spread of HIV infection. In fact, it is reported that a person who is resistant to HIV infection in spite of several exposures retains mutation of homo deletion of CCR5 gene.

        Therefore, a CCR5 antagonist is expected to be a new  
30    anti-HIV drug. However, so far, there has been no report that a CCR5 antagonist is developed as a therapeutic agent of AIDS.

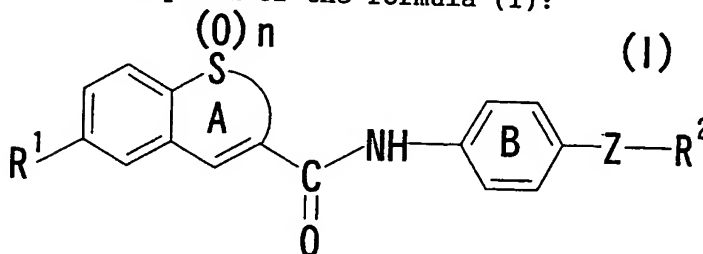
        In order to investigate an anti-AIDS drug having CCR5 antagonistic activity, it is necessary to clone CCR5 gene  
35    from human tissue derived cDNA library, to ligate said gene with a vector for expression in animal cells, to introduce

said gene into animal cells and to obtain cells expressing CCR5. In addition, with using this transformant, it is necessary to screen a compound which strongly inhibits binding of CC chemokine RANTES, natural ligand, to CCR5 (which strongly antagonizes CCR5). However, so far there has been no report on a low molecule compound having CCR5 antagonistic activity. The present invention is to provide a novel anilide derivative which is useful for the treatment or prevention of infectious disease of HIV and, in particular, AIDS and also which is suitable for oral administration, production and use thereof.

#### Disclosure of Invention

The present inventors diligently made extensive studies on compounds having CCR5 antagonistic activity and, as a result, they found that an anilide derivative of the following formula (I) or a salt thereof [hereinafter, referred to as Compound (I)] unexpectedly possesses potent CCR5 antagonistic activity and clinically desirable pharmaceutical effect (e.g. remarkable inhibition of HIV infection to human peripheral mononuclear cells, etc.) and also that Compound (I) has superior absorbability when orally administered. Based on the finding, the present invention was accomplished.

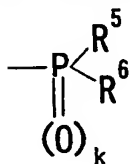
More specifically, the present invention relates to (1) A compound of the formula (I):



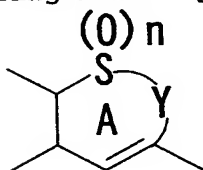
wherein R<sup>1</sup> is an optionally substituted 5- to 6-membered ring; the ring A is an optionally substituted 6- to 7-membered ring; the ring B is an optionally substituted benzene ring; n is an integer of 1 or 2; Z is a chemical



- bond or a divalent group; R<sup>2</sup> is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



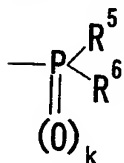
- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof; and a pro-drug of the compound or a salt thereof as described in the above (1);
- (2) A compound as described in the above (1), wherein R<sup>1</sup> is benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted;
- (3) A compound as described in the above (1), wherein R<sup>1</sup> is an optionally substituted benzene;
- (4) A compound as described in the above (1), wherein the ring A is a group of the formula:



wherein Y is  $-(\text{CH}_2)_m-$  (m is an integer of 1 or 2),  $-\text{CH}=\text{CH}-$  or  $-\text{N}=\text{CH}-$ , which may have a substituent at any possible

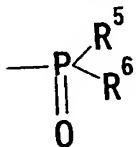
position;

- (5) A compound as described in the above (4), wherein Y is  $-(CH_2)_m-$  (m is an integer of 1 or 2);
- (6) A compound as described in the above (4), wherein Y is  $-(CH_2)_2-$ ;
- (7) A compound as described in the above (1), wherein the ring B is a benzene which may be substituted with a substituent selected from the class consisting of a halogen atom, a  $C_{1-4}$  alkyl group optionally substituted with a halogen atom and a  $C_{1-4}$  alkoxy group optionally substituted with a halogen atom;
- (8) A compound as described in the above (1), wherein n is 2;
- (9) A compound as described in the above (1), wherein Z is an optionally substituted  $C_{1-4}$  alkylene;
- (10) A compound as described in the above (1), wherein Z is a divalent group of the formula:  $-Z'-(CH_2)_{n'}-$  ( $Z'$  is  $-CH(OH)-$ ,  $-C(O)-$  or  $-CH_2-$ , and  $n'$  is an integer of 0-2) in which an optional methylene group may be substituted;
- (11) A compound as described in the above (1), wherein Z is methylene;
- (12) A compound as described in the above (1), wherein  $R^2$  is (1) an optionally substituted amino group, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms, (3) a group binding through a sulfur atom or (4) a group of the formula:



- wherein k is 0 or 1; and  $R^5$  and  $R^6$  are independently an optionally substituted hydrocarbon group or an optionally substituted amino group, and  $R^5$  and  $R^6$  may bind to each other to form a cyclic group together with the adjacent phosphorus atom;

- (13) A compound as described in the above (1), wherein R<sup>2</sup> is (1) an optionally substituted amino group, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms or (3) a group of the formula:



- wherein R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom;

- (14) A compound as described in the above (1), wherein R<sup>2</sup> is a group of the formula: -NRR'<sup>1</sup> wherein R and R' are independently an optionally substituted aliphatic hydrocarbon group (aliphatic acyclic hydrocarbon group and aliphatic cyclic hydrocarbon group) or an optionally substituted non-aromatic heterocyclic ring group;

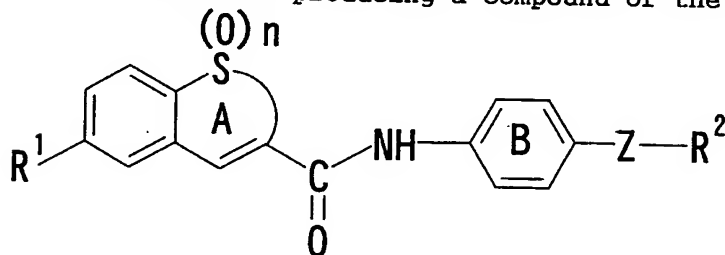
- (15) A compound as described in the above (14), wherein R is an optionally substituted acyclic hydrocarbon group and R' is an optionally substituted alicyclic hydrocarbon group (aliphatic cyclic hydrocarbon group) or an optionally substituted non-aromatic heterocyclic ring group;

- (16) A compound as described in the above (14), wherein R is an optionally substituted C<sub>1-6</sub> alkyl group and R' is an optionally substituted C<sub>3-8</sub> cycloalkyl group or an optionally substituted saturated heterocyclic ring group;

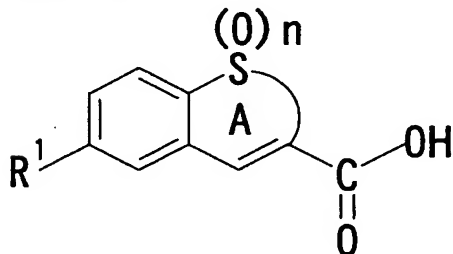
- (17) A compound as described in the above (16), wherein R' is an optionally substituted cyclohexyl, an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl;

- (18) A compound selected from the class consisting of N-[4-[N-methyl-N-(tetrahydropyran-4-

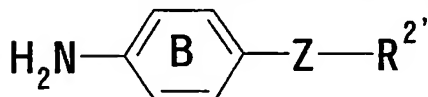
- yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide,  
7-(4-butoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-  
yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
5 benzothiepine-4-carboxamide, 7-[4-[N-methyl-N-(2-  
propoxyethyl)amino]phenyl]-N-[4-[N-methyl-N-  
(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[4-(2-  
ethoxyethoxy)phenyl]-N-[4-[N-methyl-N-  
10 (tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-  
methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-  
[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide, 7-[4-(2-  
15 butoxyethoxy)phenyl]-N-[4-[N-methyl-N-  
(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[4-(2-  
ethoxyethoxy)-3,5-dimethylphenyl]-N-[4-[N-methyl-N-  
(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-  
20 dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[2-  
chloro-4-(2-propoxyethyl)phenyl]-N-[4-[N-methyl-N-  
(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide, 7-(3-methyl-  
4-propoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-  
25 yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide and 7-(3,4-  
dipropoxyphenyl)-N-(4-((N-methyl-N-(tetrahydro-2H-  
pyran-4-yl)amino)methyl)phenyl)-1,1-dioxo-2,3-dihydro-  
1-benzothiepine-4-carboxamide; or a salt thereof;  
30 (19) A method for producing a compound of the formula:



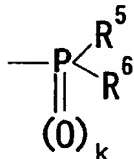
each symbol is as described in the above (1), or a salt thereof, which comprises subjecting a compound of the formula:



- 5 wherein each symbol is as described in the above (1), a salt or a reactive derivative thereof to condensation reaction with a compound of the formula:



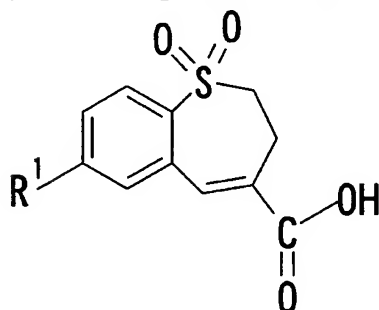
- wherein B and Z is as described in the above (1) and R<sup>2'</sup> is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium; (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium; (3) a group binding through a sulfur atom; or (4) a group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom; each of which may be protected, or a salt thereof, and, if desired, subjecting the obtained product to deprotection, oxidation,

reduction and/or ammoniation;

(20) A compound of the formula:



wherein R<sup>1</sup> is an optionally substituted 5- to 6-membered ring,  
5 or a salt thereof;

(21) A pharmaceutical composition which comprises the  
compound as described in the above (1) or a salt thereof;

(22) A composition as described in the above (21), which  
is for antagonizing CCR (preferably, CCR5);

10 (23) A composition as described in the above (21), which  
is for the treatment or prevention of infectious disease  
of HIV;

(24) A composition as described in the above (21), which  
is for the treatment or prevention of AIDS;

15 (25) A composition as described in the above (21), which  
is for the prevention of the progression of AIDS;

(26) A composition as described in the above (23), which  
is used in combination with a protease inhibitor and/or a  
reverse transcriptase inhibitor;

20 (27) A composition as described in the above (26), wherein  
the reverse transcriptase inhibitor is zidovudine,  
didanosine, zalcitabine, lamivudine, stavudine, nevirapine,  
delavirdine, efavirenz or abacavir;

(28) A composition as described in the above (26), wherein  
25 the protease inhibitor is saquinavir, ritonavir, indinavir,  
amprenavir or nelfinavir;

(29) Use of the compound as described in the above (1) or  
a salt thereof in combination with a protease inhibitor  
and/or a reverse transcriptase inhibitor for the treatment

or prevention of infectious disease of HIV;

(30) A method for antagonizing CCR which comprises administering to a mammal in need thereof an effective amount of the compound as described in the above (1) or a salt thereof;

(31) Use of the compound as described in the above (1) or a salt thereof, for the manufacture of a medicament for antagonizing CCR; etc.

- 10           In the above formula (I), examples of the "5- to 6-membered ring" of the "optionally substituted 5- to 6-membered ring" represented by R<sup>1</sup> include a 6-membered aromatic hydrocarbon such as benzene, etc.; a 5- to 6-membered aliphatic hydrocarbon (aliphatic cyclic hydrocarbon group) such as cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, etc.; 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran, etc.; etc. Among others, benzene, furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran (preferably, 6-membered ring), etc. are preferable, and in particular, benzene is

preferable.

Examples of the "substituents", which the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by  $R^1$  may have, include halogen  
5 atom, nitro, cyano, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted hydroxy group, an optionally substituted thiol group wherein a sulfur atom may be optionally oxidized to form a sulfinyl group or a sulfonyl group, an optionally  
10 substituted amino group, an optionally substituted acyl, an optionally esterified or amidated carboxyl group, an optionally substituted aromatic group, etc.

Examples of the halogen as the substituents for  $R^1$  include fluorine, chlorine, bromine, iodine, etc. Among  
15 others, fluorine and chlorine are preferable.

Examples of the alkyl in the optionally substituted alkyl as the substituents for  $R^1$  include a straight or branched  $C_{1-10}$  alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl,  
20 neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., and preferably lower ( $C_{1-6}$ ) alkyl.

Examples of the substituents in the optionally substituted alkyl include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an  
25 optionally substituted thiol group (e.g. thiol,  $C_{1-4}$  alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono- $C_{1-4}$  alkylamino, di- $C_{1-4}$  alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole,  
30 etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl,  $C_{1-4}$  alkoxy-carbonyl, carbamoyl, mono- $C_{1-4}$  alkylcarbamoyl, di- $C_{1-4}$  alkylcarbamoyl, etc.), an optionally halogenated  $C_{1-4}$  alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.),  
35 an optionally halogenated  $C_{1-4}$  alkoxy- $C_{1-4}$  alkoxy (e.g. methoxymethoxy, methoxyethoxy, ethoxyethoxy,



trifluoromethoxyethoxy, trifluoroethoxyethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the cycloalkyl in the optionally substituted cycloalkyl as the substituents for R<sup>1</sup> include C<sub>3-</sub>, cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.

Examples of the substituents in the optionally substituted cycloalkyl include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted hydroxy group as the substituents for R<sup>1</sup> include (1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.); (2) an optionally substituted cycloalkyl which may contain

- a hetero-atom (e.g. C<sub>3-7</sub>, cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; a saturated 5- to 6-membered heterocyclic ring group containing 1-2 hetero-atoms (preferably, tetrahydropyranyl, etc.) such as tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrothiopyranyl, etc.; etc.);
- 5 (3) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- 10 (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- 15 (5) an optionally substituted aralkyl (e.g. phenyl-C<sub>1-4</sub> alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (6) formyl or an optionally substituted acyl (e.g. C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- 20 (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

- Examples of the substituents which the above-mentioned
- (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl and (7) optionally substituted aryl may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g.
- 25
- 30
- 35

carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.; preferably an optionally halogenated C<sub>1-4</sub> alkoxy), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), an optionally substituted 5- to 6-membered aromatic heterocyclic ring [e.g. 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; Examples of the substituents which said heterocyclic ring may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3], etc., and the number of the substituents are preferably 1 to 3.

Examples of the substituents in the optionally substituted thiol group as the substituents for R<sup>1</sup> are similar to the above-described substituents in the optionally substituted hydroxy group as the substituents for R<sup>1</sup>, and among others,

(1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl,

heptyl, octyl, nonyl, decyl, etc., preferably lower ( $C_{1-6}$ ) alkyl, etc.);

(2) an optionally substituted cycloalkyl (e.g.  $C_{3-7}$  cycloalkyl, etc. such as cyclopropyl, cyclobutyl,

5 cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(3) an optionally substituted aralkyl (e.g. phenyl- $C_{1-4}$  alkyl (e.g. benzyl, phenethyl, etc.), etc.);

(4) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc. are preferable.

10        Examples of the substituents which the above-mentioned  
(1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted aralkyl and (4) optionally substituted aryl may have include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro,  
15 cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol,  $C_{1-4}$  alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono- $C_{1-4}$  alkylamino, di- $C_{1-4}$  alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine,  
20 thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl,  $C_{1-4}$  alkoxy-carbonyl, carbamoyl, mono- $C_{1-4}$  alkylcarbamoyl, di- $C_{1-4}$  alkylcarbamoyl, etc.), an optionally halogenated  $C_{1-4}$  alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated  $C_{1-4}$  alkoxy (e.g. methoxy,  
25 ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl,  $C_{1-4}$  alkanoyl (e.g. acetyl, propionyl, etc.),  $C_{1-4}$  alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are  
30 preferably 1 to 3.

      Examples of the substituents in the optionally substituted amino group as the substituents for  $R^1$  are similar to the above-described substituents in the optionally substituted hydroxy group as the substituents for  $R^1$ , and  
35 examples of the optionally substituted amino group as the substituents for  $R^1$  include an amino group which may have one

to two substituents selected from the above-described substituents in the optionally substituted hydroxy group as the substituents for R<sup>1</sup>, etc. Among others, as the substituents in the optionally substituted amino group as the substituents for R<sup>1</sup>,

- (1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) formyl or an optionally substituted acyl (e.g. C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc. are preferable.

Examples of the substituents, which each of the above-described (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted acyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole,

piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

The substituents in the optionally substituted amino group as the substituents for R<sup>1</sup> may bind to each other to form a cyclic amino group (e.g. 5- to 6-membered cyclic amino, etc. such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.). Said cyclic amino group may have a substituent, and examples of the substituents include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally substituted acyl as the

substituents for R<sup>1</sup> include a carbonyl group or a sulfonyl group binding to

- (1) hydrogen;
- (2) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, 5 sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
- (3) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> 10 cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (4) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- (5) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> 15 cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (6) an optionally substituted 5- to 6-membered monocyclic aromatic group (e.g. phenyl, pyridyl, etc.); etc.

- 20 Examples of the acyl include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, 25 benzoyl, nicotinoyl, methanesulfonyl, ethanesulfonyl, etc.

- Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally 30 substituted 5- to 6-membered monocyclic aromatic group may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> 35 alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine,

morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally  
5 halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl,  
10 etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally esterified carboxyl group as the substituents for R<sup>1</sup> include a carbonyloxy group binding to

- 15 (1) hydrogen;
- (2) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>)  
20 alkyl, etc.);
- (3) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (4) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such  
25 as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- (5) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- 30 (6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc., and preferably carboxyl, lower (C<sub>1-6</sub>) alkoxy-carbonyl, aryloxy-carbonyl (e.g. methoxy-carbonyl, ethoxy-carbonyl, propoxy-carbonyl, phenoxy-carbonyl, naphthoxy-carbonyl, etc.), etc.

35 Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally



substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.); etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally amidated carboxyl group as the substituents for R<sup>1</sup> include an carbonyl group binding to an optionally substituted amino group, etc. which is similar to the above-described "optionally substituted amino group as the substituents for R<sup>1</sup>", and among others, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc. are preferable.

Examples of the aromatic group in the optionally substituted aromatic group as the substituents for R<sup>1</sup> include 5- to 6-membered aromatic homocyclic or heterocyclic ring such as phenyl, pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, etc.; fused aromatic heterocyclic ring such as benzofuran, indole, benzothiophene, benzoxazole, benzothiazole, indazole, benzimidazole,

quinoline, isoquinoline, quinoxaline, phthalazine, quinazoline, cinnoline, etc.; etc.

Examples of the substituents for these aromatic group include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>1-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

The number of the above-mentioned substituents for R<sup>1</sup> is 1-4 (preferably 1-2) and they may be same or different and present at any possible position on the ring represented by R<sup>1</sup>. When two or more substituents are present on the 5- to 6-membered ring in the "an optionally substituted 5- to 6-membered ring" represented by R<sup>1</sup>, two substituents among them may bind to each other to form a lower (C<sub>1-6</sub>) alkylene (e.g. trimethylene, tetramethylene, etc.), a lower (C<sub>1-6</sub>) alkyleneoxy (e.g. -CH<sub>2</sub>-O-CH<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -O-CH(CH<sub>3</sub>)(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, etc.), a lower (C<sub>1-6</sub>) alkylenethio (e.g. -CH<sub>2</sub>-S-CH<sub>2</sub>-, -S-CH<sub>2</sub>-CH<sub>2</sub>-, -S-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -S-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -S-CH(CH<sub>3</sub>)(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>2</sub>-, etc.), a lower (C<sub>1-6</sub>) alkylenedioxy (e.g. -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-O-, etc.), a lower (C<sub>1-6</sub>) alkylenedithio (e.g. -S-CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-CH<sub>2</sub>-S-, -S-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-S-, etc.), an oxy-lower (C<sub>1-6</sub>) alkylene-amino (e.g. -O-CH<sub>2</sub>-NH-, -O-CH<sub>2</sub>-

CH<sub>2</sub>-NH-, etc.), an oxy-lower (C<sub>1-6</sub>) alkylene-thio (e.g. -O-CH<sub>2</sub>-S-, -O-CH<sub>2</sub>-CH<sub>2</sub>-S-, etc.), a lower (C<sub>1-6</sub>) alkylene-amino (e.g. -NH-CH<sub>2</sub>-CH<sub>2</sub>-, -NH-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, etc.), a lower (C<sub>1-6</sub>) alkylene-diamino (e.g. -NH-CH<sub>2</sub>-NH-, -NH-CH<sub>2</sub>-CH<sub>2</sub>-NH-, etc.),  
 5 a thia-lower (C<sub>1-6</sub>) alkylene-amino (e.g. -S-CH<sub>2</sub>-NH-, -S-CH<sub>2</sub>-CH<sub>2</sub>-NH-, etc.), a lower (C<sub>2-6</sub>) alkenylene (e.g. -CH<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-CH<sub>2</sub>-CH=CH-, -CH<sub>2</sub>-CH=CH-CH<sub>2</sub>-, etc.), a lower (C<sub>4-6</sub>) alkadienylene (e.g. -CH=CH-CH=CH-, etc.), etc.

When two substituents of R<sup>1</sup> bind to each other to form  
 10 a divalent group containing a hetero-atom (oxygen atom, sulfur atom, nitrogen atom, etc.), said divalent group may contain an unsaturated bond. Examples of the divalent group containing a hetero-atom and an unsaturated bond include  
 15 -O-CH=CH-, -O-CH=CH-CH<sub>2</sub>-, -O-CH<sub>2</sub>-CH=CH-, -S-CH=CH-, -S-CH=CH-CH<sub>2</sub>-, -S-CH<sub>2</sub>-CH=CH-, -O-CH=CH-O-, -O-CH=CH-CH<sub>2</sub>-O-,  
 -S-CH=CH-S-, -S-CH=CH-CH<sub>2</sub>-S-, -O-CH=N-, -O-CH<sub>2</sub>-CH=N-, -O-CH=CH-NH-, -S-CH=N-, -S-CH<sub>2</sub>-CH=N-, -S-CH=CH-NH-, -O-CH=CH-S-, -N=CH-CH<sub>2</sub>-, -NH-CH=CH-, -N=CH-CH<sub>2</sub>-CH<sub>2</sub>-, -NH-CH=CH-CH<sub>2</sub>-, -NH-CH<sub>2</sub>-CH=CH-, -N=CH-NH-, -NH-CH=CH-NH-,  
 20 N=CH-CH<sub>2</sub>-NH-, (preferably, -O-CH=CH-, -S-CH=CH-, -O-CH=N-, -S-CH=N-, etc.), etc.

The divalent group formed by two substituents of R<sup>1</sup> binding to each other may have 1-3 substituents similar to the substituents, which the "5- to 6-membered ring" in the  
 25 "optionally substituted 5- to 6-membered ring" represented by R<sup>1</sup> may have, such as halogen atom, nitro, cyano, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted hydroxy group, an optionally substituted thiol group wherein a sulfur atom  
 30 may be optionally oxidized to form a sulfinyl group or a sulfonyl group, an optionally substituted amino group, an optionally substituted acyl, an optionally esterified or amidated carboxyl group, an optionally substituted aromatic group, etc.

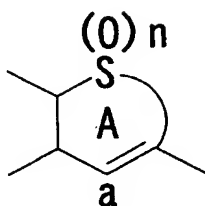
35 Preferred examples of the "substituents", which the "5- to 6-membered ring" in the "an optionally substituted

- 5- to 6-membered ring" represented by R<sup>1</sup> may have, include a lower (C<sub>1-4</sub>) alkyl optionally substituted with a halogen or a lower (C<sub>1-4</sub>) alkoxy (e.g. methyl, ethyl, t-butyl, trifluoromethyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, methoxyethyl, ethoxyethyl, propoxyethyl, butoxyethyl, etc.), a lower (C<sub>1-4</sub>) alkoxy optionally substituted with a halogen or a lower (C<sub>1-4</sub>) alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, methoxyethoxy, ethoxyethoxy, propoxyethoxy, butoxyethoxy, methoxypropoxy, ethoxypropoxy, propoxypropoxy, butoxypropoxy, etc.), halogen (e.g. fluorine, chlorine, etc.), nitro, cyano, an amino group optionally substituted with 1-2 lower (C<sub>1-4</sub>) alkyl groups, lower (C<sub>1-4</sub>) alkoxy-lower (C<sub>1-4</sub>) alkyl groups, formyl groups or lower (C<sub>2-4</sub>) alkanoyl groups (e.g. amino, methylamino, dimethylamino, formylamino, acetylamino, etc.), 5- to 6-membered cyclic amino (e.g. 1-pyrrolidinyl, 1-piperazinyl, 1-piperidinyl, 4-morpholino, 4-thiomorpholino, 1-imidazolyl, 4-tetrahydropyranyl, etc.), etc., and when R<sup>1</sup> is a benzene, the "substituent" is preferably present at para position.

In the above formula (I), examples of the substituents which the "6- to 7-membered ring" in the "optionally substituted 6- to 7-membered ring" represented by A may have are similar to those which the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R<sup>1</sup> may have

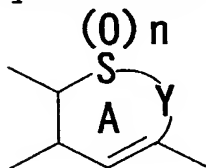
- The number of said substituents for the ring A is 1-3 (preferably 1-2), and they may be same or different and present at any possible position on the ring represented by A.

In the group of the formula:



represented by A, a carbon atom at the position a is preferably unsubstituted.

- 5 Examples of the "6- to 7-membered ring" in the "optionally substituted 6- to 7-membered ring" represented by A include a 6- to 7-membered ring group of the formula:



, which may have a substituent at any possible position, etc.

- 10 In the above formula, the divalent group represented by Y may be any divalent group as far as the ring A forms an optionally substituted 6- to 7-membered ring, and preferred examples of the divalent groups include

- (1)  $-\text{CH}_2-\text{O}-$ ;  
 (2)  $-\text{CH}_2-\text{S}-$ ;  
 15 (3)  $-(\text{CH}_2)_{d_1}-$  ( $d_1$  is 1 or 2),  $-\text{CH}=\text{CH}-$ ;  
 (4)  $-(\text{CH}_2)_{e_1}-\text{NH}-(\text{CH}_2)_{e_2}-$  ( $e_1$  and  $e_2$  are same or different and one of them is 0 and the other one is 0 or 1),  $-\text{N}=\text{CH}-$ ,  $-\text{CH}=\text{N}-$ ;  
 etc. More preferred examples of the divalent groups include  
 $-\text{CH}_2-\text{O}-$ ,  $-\text{CH}_2-\text{S}-$ ,  $\text{CH}_2-$ ,  $-(\text{CH}_2)_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{NH}-$ ,  $-\text{N}=\text{CH}-$ ,  $-\text{CH}=\text{N}-$ , etc.  
 20

- The divalent group may have a substituent. Examples of the substituent include those for the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by  $\text{R}^1$  and an oxo group, etc. Among others, a  
 25 lower ( $\text{C}_{1-3}$ ) alkyl (e.g. methyl, ethyl, propyl, etc.), a phenyl group, an oxo group, a hydroxy group, etc. are preferable. In addition, the divalent group may be  $-\text{O}-\text{C}(\text{O})-$ , etc. The number of the substituents are preferably 1 to 2,

and they may be same or different and bind to the divalent group at any possible position.

As the divalent group represented by Y, a group of the formula:  $-(CH_2)_m-$  (m is an integer of 1 or 2),  $-CH=CH-$ ,  $-N=CH-$ , etc. is preferable. Among others, a group of the formula:  $-(CH_2)_m-$  (m is an integer of 1 or 2), etc. is preferable. In particular, Y is preferably  $-(CH_2)_2-$ .

Examples of the "substituents", which the "benzene ring" in the "optionally substituted benzene ring" represented by B may have, include those for the "5- to 6-membered ring" in the "optionally substituted 5- to 6-membered ring" represented by R<sup>1</sup>, etc. Among others, halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc. are preferable and in particular, halogen, an optionally halogenated C<sub>1-4</sub> alkyl, an optionally halogenated C<sub>1-4</sub> alkoxy, etc. are preferable. The number of the substituents are preferably 1 to 3.

In the above formula (I), n is an integer of 1 or 2 (preferably, 2).

In the above formula (I), examples of the divalent group represented by Z include an optionally substituted divalent group whose straight chain is constituted by 1 to 4 carbon

atoms (e.g.  $C_{1-4}$  alkylene,  $C_{2-4}$  alkenylene, etc., preferably  $C_{1-3}$  alkylene, more preferably methylene), etc.

The divalent group represented by Z may be any divalent group whose straight chain is constituted by 1 to 4 atoms and exemplified by an alkylene chain of the formula:  
5  $-(CH_2)_{k_1}-$  ( $k_1$  is an integer of 1-4), an alkenylene chain of the formula:  $-(CH_2)_{k_2}-(CH=CH)-(CH_2)_{k_3}-$  ( $k_2$  and  $k_3$  are same or different and 0, 1 or 2, provided that the sum of  $k_2$  and  $k_3$  is 2 or less), etc.

10 Examples of the substituent for the divalent group represented by Z include any one which is capable of binding to the straight chain of the divalent group, and preferably  $C_{1-6}$  lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl,  
15 neopentyl, hexyl, etc.), lower ( $C_{3-7}$ ) cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.), formyl, lower ( $C_{2-7}$ ) alkanoyl (e.g. acetyl, propionyl, butyryl, etc.), an optionally esterified phosphono group, an optionally esterified carboxyl group,  
20 hydroxy group, oxo, etc., and more preferably  $C_{1-6}$  lower alkyl (preferably  $C_{1-3}$  alkyl), hydroxy group, oxo, etc.

Examples of the optionally esterified phosphono group include a group of the formula:  $P(O)(OR')(OR'')$  wherein  $R'$  and  $R''$  are independently hydrogen, a  $C_{1-6}$  alkyl group or a  $C_{3-7}$   
25 cycloalkyl group, and  $R'$  and  $R''$  may bind to each other to form a 5- to 7-membered ring.

In the above formula, examples of the  $C_{1-6}$  alkyl group represented by  $R'$  and  $R''$  include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl,  
30 isopentyl, neopentyl, hexyl, etc., and examples of the  $C_{3-7}$  cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. Among other, a straight  $C_{1-6}$  lower alkyl is preferable and  $C_{1-3}$  lower alkyl is more preferable. The groups  $R'$  and  $R''$  may be same or different,  
35 and preferably the groups  $R'$  and  $R''$  are same. When  $R'$  and  $R''$  may bind to each other to form a 5- to 7-membered ring,

the groups R' and R' bind to each other to represent a straight C<sub>2-4</sub> alkylene chain of the formula: -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-, etc. Said chain may have a substituent, and examples of the substituent include hydroxy group, halogen, etc.

5        Examples of the optionally esterified carboxyl group include a carboxyl group and an ester group formed by binding a carboxyl group to a C<sub>1-6</sub> alkyl group or a C<sub>3-7</sub> cycloalkyl group (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, 10 isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.).

      As the divalent group represented by Z, an optionally substituted C<sub>1-3</sub> alkylene is preferable, and C<sub>1-3</sub> alkylene which may be substituted by C<sub>1-3</sub> alkyl, hydroxy group or oxo 15 is more preferable.

      Among others, as the divalent group represented by Z, a group of the formula: -Z'-(CH<sub>2</sub>)<sub>n</sub>'- or -(CH<sub>2</sub>)<sub>n</sub>'-Z' (Z' is -CH(OH)-, -C(O)- or -CH<sub>2</sub>-, and n' is an integer of 0-2) in which each of the above formulas represent that it binds 20 to the benzene ring through its left chemical bond and each of the methylene groups may be substituted by 1-2 same or different substituents is preferable, a group of the formula: -Z'-(CH<sub>2</sub>)<sub>n</sub>'- (Z' is -CH(OH)-, -C(O)- or -CH<sub>2</sub>-, and n' is an integer of 0-2 (preferably, n is 0)) in which the 25 formula binds to the benzene ring through its left chemical bond and each of the methylene groups may be substituted by 1-2 same or different substituents is more preferable, and methylene is particularly preferable.

      In the above-mentioned formula (I), examples of the 30 "amino group" in the "optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium (preferably, optionally substituted amino group)" represented by R' include an amino group which may have 1-2 substituents, an amino group having 3 substituents wherein 35 the nitrogen atom forms a quaternary ammonium, etc. When the number of the substituents on the nitrogen atom is 2



or more, these substituents may be same or different. When the total number of the substituents and hydrogen atoms on the nitrogen atom is 3, the "amino group" represented by  $R^2$  may be any type of an amino group represented by the formula:  $-N^+R_3$ ,  $-N^+R_2R'$  or  $-N^+RR'R''$  ( $R$ ,  $R'$  and  $R''$  are independently a hydrogen atom or a substituent). Examples of the counter anion of the amino group wherein the nitrogen atom forms a quaternary ammonium include an anion of a halogen atom (e.g.  $Cl^-$ ,  $Br^-$ ,  $I^-$ , etc.), etc., and also an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; an anion derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others,  $Cl^-$ ,  $Br^-$ ,  $I^-$ , etc. are preferable.

Examples of the substituents for said amino group include

- (1) an optionally substituted alkyl (e.g.  $C_{1-10}$  alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower ( $C_{1-6}$ ) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g.  $C_{3-8}$  cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.), provided that

- (2-1) said cycloalkyl may contain one hetero-atom selected from a sulfur atom, an oxygen atom and a nitrogen atom to form oxirane, thiorane, aziridine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran 1-oxide, piperidine, etc. (preferably, 6-membered ring such as

- tetrahydropyran, tetrahydrothiopyran, piperidine, etc.) and these groups preferably bind to the amino group at their 3- or 4-position (preferably, 4-position), that (2-2) said cycloalkyl may be fused with a benzene ring to form indane, tetrahydronaphthalene, etc. (preferably, indane, etc.), and that (2-3) said cycloalkyl may have a bridging comprising a straight chain constituted by 1-2 carbon atoms to form a bridged hydrocarbon residue such as bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, etc., preferably, a cyclohexyl group, etc. having a bridging comprising a straight chain constituted by 1-2 carbon atoms, and more preferably bicyclo[2.2.1]heptyl, etc.;
- (3) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) an optionally substituted aralkyl (e.g. phenyl-C<sub>1-4</sub> alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (6) formyl or an optionally substituted acyl (e.g. C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.);
- (8) an optionally substituted heterocyclic ring group (e.g. 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring

- containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline,
- 5 imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, etc.; etc.; preferably 5- to 6-membered non-aromatic heterocyclic ring, etc.; more preferably 5-
- 10 to 6-membered non-aromatic heterocyclic ring; further more preferably 5- to 6-membered non-aromatic heterocyclic ring containing one hetero-atom, etc. such as tetrahydrofuran, piperidine, tetrahydropyran, tetrahydrothiopyran, etc.); etc.
- 15 In addition, the substituents for the amino group may bind to each other to form a 5- to 7-membered cyclic amino group such as piperidine, piperazine, morpholine, thiomorpholine, etc.

- Examples of the substituents, which the above-
- 20 mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl, (7) optionally substituted aryl and (8) optionally substituted
- 25 heterocyclic ring group may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), an optionally halogenated lower (C<sub>1-4</sub>) alkyl, an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), C<sub>1-4</sub>
- 30 alkylenedioxy (e.g. -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), phenyl-lower (C<sub>1-4</sub>) alkyl, C<sub>3-7</sub> cycloalkyl, cyano, nitro, hydroxy group, an optionally substituted thiol group (e.g.
- 35 thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino,

5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), lower (C<sub>1-4</sub>) alkoxy-carbonyl, oxo (preferably, halogen, an optionally halogenated lower (C<sub>1-4</sub>) alkyl, an optionally halogenated lower (C<sub>1-4</sub>) alkoxy, phenyl-lower (C<sub>1-4</sub>) alkyl, C<sub>3-</sub>, cycloalkyl, cyano, hydroxy group, etc.), etc., and the number of the substituents are preferably 1 to 3.

In the above formula (I), preferred examples of the "optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium" represented by R<sup>2</sup> include

15 an amino group which may have 1-3 substituents (preferably 1-2 substituents) selected from the class consisting of

(1) a straight or branched lower (C<sub>1-6</sub>) alkyl which may have 1 to 3 substituents selected from halogen, cyano, hydroxy group or C<sub>3-</sub>, cycloalkyl;

20 (2) a C<sub>5-8</sub>cycloalkyl which may have 1 to 3 substituents selected from halogen, an optionally halogenated lower (C<sub>1-4</sub>) alkyl or phenyl-lower (C<sub>1-4</sub>) alkyl, which may contain one hetero-atom selected from a sulfur atom, an oxygen atom and a nitrogen atom, which may be fused with a benzene ring,

25 and which may have a bridging comprising a straight chain constituted by 1-2 carbon atoms (e.g. cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, tetrahydrothiapyranyl, piperidinyl, indanyl, tetrahydronaphthalenyl, bicyclo[2.2.1]heptyl, etc., each

30 of which may be substituted);

(3) a phenyl-lower (C<sub>1-4</sub>) alkyl which may have 1 to 3 substituents selected from halogen, an optionally halogenated lower (C<sub>1-4</sub>) alkyl or an optionally halogenated lower (C<sub>1-4</sub>) alkoxy;

35 (4) a phenyl which may have 1 to 3 substituents selected from halogen, an optionally halogenated lower (C<sub>1-4</sub>) alkyl

or an optionally halogenated lower (C<sub>1-4</sub>) alkoxy; and  
(5) a 5- to 6-membered aromatic heterocyclic ring (e.g. furan,  
thiophene, pyrrole, pyridine, etc.) which may have 1 to 3  
substituents selected from halogen, an optionally  
5 halogenated lower (C<sub>1-4</sub>) alkyl, an optionally halogenated  
lower (C<sub>1-4</sub>) alkoxy, an optionally halogenated lower (C<sub>1-4</sub>)  
alkoxy-lower (C<sub>1-4</sub>) alkoxy, phenyl-lower (C<sub>1-4</sub>) alkyl, cyano  
or hydroxy group.

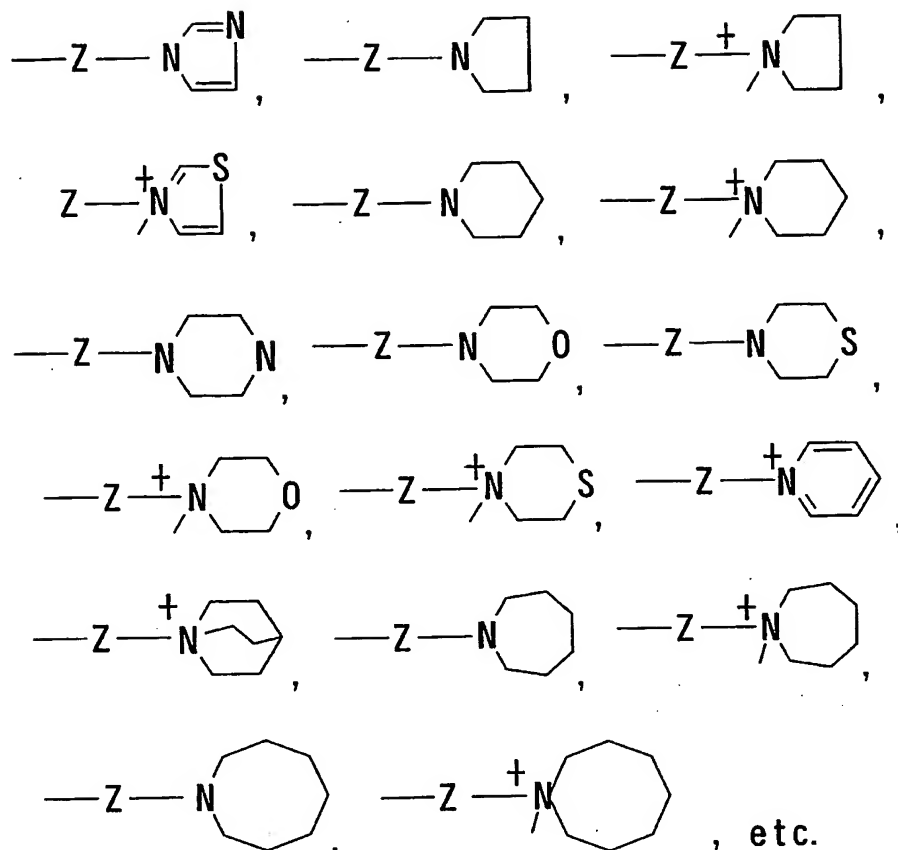
In the above formula (I), examples of the "nitrogen-  
10 containing heterocyclic ring" in the "optionally  
substituted nitrogen-containing heterocyclic ring group  
which may contain a sulfur atom or an oxygen atom as ring  
constituting atoms and wherein a nitrogen atom may form a  
quaternary ammonium (preferably, optionally substituted  
15 nitrogen-containing heterocyclic ring group which may  
contain a sulfur atom or an oxygen atom as ring constituting  
atoms)" include a 5- to 6-membered aromatic heterocyclic  
ring which may contain 1 to 3 hetero-atoms consisting of  
1 to 2 kinds of hetero-atoms selected from an oxygen atom,  
20 a sulfur atom and a nitrogen atom other than one nitrogen  
atom such as pyrrole, imidazole, pyrazole, thiazole, oxazole,  
isothiazole, isoxazole, tetrazole, pyridine, pyrazine,  
pyrimidine, pyridazine, triazole, etc.; 5-8 membered  
non-aromatic heterocyclic ring which may contain 1 to 3  
25 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms  
selected from an oxygen atom, a sulfur atom and a nitrogen  
atom other than one nitrogen atom such as pyrrolidine,  
pyrroline, imidazolidine, imidazoline, pyrazolidine,  
pyrazoline, piperidine, piperazine, oxazine, oxadiazine,  
30 thiazine, thiadiazine, morpholine, thio-morpholine,  
azacycloheptane, azacyclooctane (azocane), etc.; etc.  
These nitrogen-containing heterocyclic rings may have a  
bridging comprising a straight chain constituted by 1-2  
carbon atoms to form a bridged nitrogen-containing  
35 heterocyclic ring azabicyclo[2.2.1]heptane,  
azabicyclo[2.2.2]octane (quinuclidine), etc. (preferably,

piperidine having a bridging comprising a straight chain constituted by 1-2 carbon atoms, etc.).

Among the above-exemplified nitrogen-containing heterocyclic rings, pyridine, imidazole, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, azabicyclo[2.2.2]octane (preferably, a 6-membered ring) are preferable.

The nitrogen atom of said "nitrogen-containing heterocyclic ring" may form a quaternary ammonium or may be oxidized. When the nitrogen atom of said "nitrogen-containing heterocyclic ring" forms a quaternary ammonium, examples of the counter anion of the "nitrogen-containing heterocyclic ring wherein the nitrogen atom forms a quaternary ammonium" include an anion of a halogen atom (e.g.  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ , etc.), etc., and also an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; an anion derived from an organic acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; an anion derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ , etc. are preferable.

Said "nitrogen-containing heterocyclic ring" may bind to the divalent group represented by Z through either a carbon atom or a nitrogen atom, and may be 2-pyridyl, 3-pyridyl, 2-piperidinyl, etc. which binds to the divalent group represented by Z through a carbon atoms. Preferably, the "nitrogen-containing heterocyclic ring" binds to the divalent group represented by Z through a nitrogen atom, as exemplified by the following formulas:



Examples of the substituents, which said "nitrogen containing heterocyclic ring" may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), an optionally substituted lower ( $C_{1-4}$ ) alkyl, an optionally substituted lower ( $C_{1-4}$ ) alkoxy, an optionally substituted phenyl, an optionally substituted mono- or di-phenyl-lower ( $C_{1-4}$ ) alkyl, an optionally substituted  $C_{3-7}$  cycloalkyl, cyano, nitro, hydroxy group, an optionally substituted thiol group (e.g. thiol,  $C_{1-4}$  alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono- $C_{1-4}$  alkylamino, di- $C_{1-4}$  alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl,  $C_{1-4}$  alkoxy-

carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), lower (C<sub>1-4</sub>) alkoxy-carbonyl, formyl, lower (C<sub>2-4</sub>) alkanoyl, lower (C<sub>1-4</sub>) alkylsulfonyl, an optionally substituted heterocyclic ring group (e.g. 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; 5- to 6-membered non-aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom such as tetrahydrofuran, tetrahydrothiophene, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, tetrahydrothiopyran, etc.; etc.), etc., and the number of the substituents is preferably 1-3.

Examples of the substituent, which the "optionally substituted lower (C<sub>1-4</sub>) alkyl", the "optionally substituted lower (C<sub>1-4</sub>) alkoxy", the "optionally substituted phenyl", the "optionally substituted mono- or di-phenyl-lower (C<sub>1-4</sub>) alkyl", the "optionally substituted C<sub>3-7</sub> cycloalkyl" and the "optionally substituted heterocyclic ring group" as a substituent for said "nitrogen-containing heterocyclic ring" may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), an optionally halogenated lower (C<sub>1-4</sub>) alkyl, lower (C<sub>3-10</sub>) cycloalkyl, lower (C<sub>3-10</sub>) cycloalkenyl, an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), C<sub>1-3</sub> alkylenedioxy (e.g. methylenedioxy, ethylenedioxy,



etc.), cyano, nitro, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino  
5 such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), lower (C<sub>1-4</sub>)  
10 alkoxy-carbonyl, etc., and the number of the substituents are preferably 1 to 3. In addition, the nitrogen atom in said "nitrogen-containing heterocyclic ring" may be oxidized.

In the above formula (I), preferred example of the  
15 substituents for the "nitrogen-containing heterocyclic ring" in the "optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a  
nitrogen atom may form a quaternary ammonium" include  
20 (1) halogen, (2) cyano, (3) hydroxy group, (4) carboxyl group, (5) lower (C<sub>1-4</sub>) alkoxy-carbonyl, (6) lower (C<sub>1-4</sub>) alkyl which may be substituted with halogen, hydroxy group or lower (C<sub>1-4</sub>) alkoxy, (7) lower (C<sub>1-4</sub>) alkoxy which may be substituted with  
halogen, hydroxy group or lower (C<sub>1-4</sub>) alkoxy, (8) phenyl  
25 which may be substituted with halogen, lower (C<sub>1-4</sub>) alkyl, hydroxy group, lower (C<sub>1-4</sub>) alkoxy or C<sub>1-3</sub> alkylenedioxy, (9) mono- or di-phenyl-lower (C<sub>1-4</sub>) alkyl whose benzene ring may be substituted with halogen, lower (C<sub>1-4</sub>) alkyl, hydroxy group, lower (C<sub>1-4</sub>) alkoxy or C<sub>1-3</sub> alkylenedioxy, (10) 5- to 6-membered  
30 aromatic heterocyclic ring such as furan, thiophene, pyrrole, pyridine, etc., etc.

In the above formula (I), examples of the "group binding through a sulfur atom" represented by R<sup>2</sup> include a group of the formula: -S(O)<sub>m</sub>-R<sup>s</sup> wherein m is an integer of 0-2, and  
35 R<sup>s</sup> is a substituent.

In the above formula, preferred examples of the

"substituent" represented by R<sup>s</sup> include

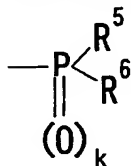
- (1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted aralkyl (e.g. phenyl-C<sub>1-4</sub> alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (4) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.) etc.

Examples of the substituent, which the above-mentioned

- (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted aralkyl and (4) an optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

- In the above formula (I), examples of the "hydrocarbon group" in the "optionally substituted hydrocarbon group"

represented by R<sup>5</sup> and R<sup>6</sup> of the "group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium (preferably, a phosphorus atom does not form a phosphonium); and R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group (preferably, an optionally substituted hydrocarbon group or an optionally substituted amino group), and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom" represented by R<sup>2</sup> include
- (1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
  - (2) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
  - (3) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
  - (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
  - (5) an optionally substituted alkynyl (e.g. C<sub>2-10</sub> alkynyl such as ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-pentynyl, 3-hexynyl, etc., preferably lower (C<sub>2-6</sub>) alkynyl, etc.);
  - (6) an optionally substituted aralkyl (e.g. phenyl-C<sub>1</sub> alkyl (e.g. benzyl, phenethyl, etc.), etc.);
  - (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents, which the above-

mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted alkynyl, (6) optionally substituted aralkyl and (7) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the "optionally substituted hydroxy group" represented by R<sup>5</sup> and R<sup>6</sup> include a hydroxy group which may have

- (1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);

- (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- 5 (5) an optionally substituted aralkyl (e.g. phenyl-C<sub>1-4</sub> alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- (6) formyl or an optionally substituted acyl (e.g. C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- 10 (7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents, which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl,

15 (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl and (7) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group

20 (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an

25 optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy,

30 ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

35 Examples of the "optionally substituted amino group" represented by R<sup>5</sup> and R<sup>6</sup> include an amino group which may

have

- (1) an optionally substituted alkyl (e.g. C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g. C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g. C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) formyl or an optionally substituted acyl (e.g. C<sub>2-4</sub> alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (6) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents, which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted acyl and (6) optionally substituted aryl may have, include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally

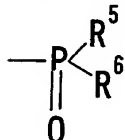
halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>1-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.),  
5 C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

In the above formula, the groups R<sup>3</sup> and R<sup>4</sup> may bind to each other to form a cyclic group (preferably, 5- to 7-  
10 membered ring) together with the adjacent phosphorus atom. Said cyclic group may have a substituent. Examples of the substituent include halogen (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g. thiol, C<sub>1-4</sub>  
15 alkylthio, etc.), an optionally substituted amino group (e.g. amino, mono-C<sub>1-4</sub> alkylamino, di-C<sub>1-4</sub> alkylamino, 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc., etc.), an optionally esterified or amidated carboxyl  
20 group (e.g. carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g. trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>1-4</sub> alkanoyl (e.g. acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the  
25 substituents are preferably 1 to 3.

In the above formula (I), examples of the counter anion,  
30 when the phosphorus atom forms a phosphonium, include an anion of a halogen atom (e.g. Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, etc.), etc., and also an anion derived from an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.; an anion derived from an organic  
35 acid such as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid,

citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.; an anion derived from an acidic amino acid such as aspartic acid, glutamic acid, etc.; etc. Among others,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ , etc. are preferable.

As the group  $\text{R}^2$ , (1) an optionally substituted amino group wherein a nitrogen atom may form a quaternary ammonium (preferably, an optionally substituted amino group), (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium (preferably, an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms) and (3) a group of the formula:



wherein  $\text{R}^5$  and  $\text{R}^6$  are independently an optionally substituted hydrocarbon group, and  $\text{R}^5$  and  $\text{R}^6$  may bind to each other to form a cyclic group together with the adjacent phosphorus atom are preferable.

As the group  $\text{R}^2$ , (1) an optionally substituted amino group in which a nitrogen atom do not form a quaternary ammonium is preferable, and a group of the formula:  $-\text{NRR}'$  wherein R and  $\text{R}'$  are independently an optionally substituted aliphatic (acyclic and alicyclic) hydrocarbon group or an optionally substituted alicyclic (non-aromatic) heterocyclic ring group is more preferable.

Examples of the "optionally substituted aliphatic hydrocarbon group" and the "optionally substituted alicyclic heterocyclic ring group" represented by R or  $\text{R}'$  include

the "optionally substituted aliphatic (non-aromatic) hydrocarbon group" (e.g. alkyl, cycloalkyl, alkenyl,



cycloalkenyl, etc., each of which may be substituted) and the "optionally substituted alicyclic heterocyclic ring group" (e.g. an optionally substituted 5- to 6-membered non-aromatic heterocyclic ring, etc.), respectively  
5 exemplified by the substituents for the "optionally substituted amino" represented by R<sup>2</sup>.

Among them, as the group R, an optionally substituted acyclic hydrocarbon group (e.g. alkyl, alkenyl, etc., each of which may be substituted) is preferable, an optionally  
10 substituted C<sub>1-6</sub> alkyl group is more preferable, and an optionally substituted methyl is most preferable; and as the group R', an optionally substituted acyclic hydrocarbon group (e.g. alkyl, alkenyl, etc., each of which may be substituted; more preferably, an optionally substituted C<sub>1-6</sub>  
15 alkyl group; further more preferably, an optionally substituted ethyl), an optionally substituted alicyclic hydrocarbon group (e.g. cycloalkyl, cycloalkenyl, etc., each of which may be substituted; more preferably, an optionally substituted C<sub>3-8</sub> cycloalkyl group; further more  
20 preferably, an optionally substituted cyclohexyl) or an optionally substituted alicyclic (non-aromatic) heterocyclic ring group (more preferably, an optionally substituted saturated heterocyclic ring group (preferably 6-membered ring group); further more preferably, an  
25 optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl; most preferably, an optionally substituted tetrahydropyranyl) is preferable.

Among them, as the group R', an optionally substituted  
30 alicyclic hydrocarbon group or an optionally substituted alicyclic (non-aromatic) heterocyclic ring group is preferable.

Examples of the salts of the compound represented by the formula (I) include a pharmaceutically acceptable salt  
35 such as a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt

with basic or acidic amino acid, etc. Examples of the salt with the inorganic base include a salt with alkali metal (e.g. sodium, potassium, etc.), alkaline earth metal (e.g. calcium, magnesium, etc.), aluminum, ammonium, etc.

5 Examples of the salt with the organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc.

10 Examples of the salt with the inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Examples of the salt with the organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Examples of the salt with the basic amino acid include a salt with arginine, lysine, ornithine, etc. Examples of the salt with the acidic amino acid include a salt with aspartic acid, glutamic acid, etc.

20 The compound of the formula (I) of the present invention may be hydrated or solvated. When the compound of the formula (I) of the present invention exists as configuration isomer, diastereomer, conformer, etc., it is possible to isolate individual isomers with per se known separation and purification method, if desired. When the compound of the formula (I) of the present invention is racemate, it can be separated into (S)-compound and (R)-compound with usual optical resolution and individual optical isomers and a mixture thereof are included in the scope of the present invention.

30 The pro-drug of the compound of the formula (I) or a salt thereof of the present invention [hereinafter, referred to as Compound (I)] means a compound which is converted to Compound (I) under the physiological condition or with a reaction due to an enzyme, an gastric acid, etc. in the living body, that is, a compound which is converted to Compound (I)

with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to Compound (I) with gastric acid, etc.; etc.

Examples of the pro-drug of Compound (I) include a  
5 compound wherein an amino group of Compound (I) is substituted with acyl, alkyl, phosphoric acid, etc. (e.g. a compound wherein an amino group of Compound (I) is substituted with eicosanoyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl,  
10 tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl, etc.); a compound wherein an hydroxy group of Compound (I) is substituted with acyl, alkyl, phosphoric acid, boric acid, etc. (e.g. a compound wherein an hydroxy group of Compound (I) is substituted with acetyl, palmitoyl,  
15 propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl, etc.); a compound wherein a carboxyl group of Compound (I) is modified with ester, amide, etc. (e.g. a compound wherein a carboxyl group of Compound (I) is modified with ethyl ester, phenyl ester,  
20 carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, methyl amide, etc.); etc. These pro-drug can be produced by per  
25 se known method from Compound (I).

The pro-drug of Compound (I) may be a compound which is converted into Compound (I) under the physiological conditions as described in "Pharmaceutical Research and Development", Vol. 7 (Drug Design), pages 163-198 published  
30 in 1990 by Hirokawa Publishing Co. (Tokyo, Japan).

Compound (I) may be labeled with isotope (e.g.  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{35}\text{S}$ ,  $^{125}\text{I}$ , etc.), etc.

The present compound of the formula (I) or a salt thereof (hereinafter, "Compound (I)" include the compound  
35 of the formula (I) and its salt) alone or as an admixture with a pharmaceutically acceptable carrier (e.g. solid

formulations such as tablets, capsules, granules, powders, etc.; liquid formulations such as syrups, injections, etc.) may be orally or non-orally administered.

5 Examples of non-oral formulations include injections, drops, suppositories, pessaries, etc. In particular, pessary is useful for the prevention of infectious disease of HIV.

10 Examples of the carriers include various organic or inorganic carriers which are generally used in this field. For example, an excipient, a lubricant, a binder, an disintegrating agent, etc. are used in the solid formulations, and a solvent, a solubilizer, a suspending agent, a isotonizing agent, a buffer, a soothing agent, etc. are used in the liquid formulations. In addition, if desired, an  
15 appropriate additive such as a preservative, an antioxidant, a colorant, a sweetener, etc. may be used in the above formulations.

Examples of the excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silic acid  
20 anhydride, etc. Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, etc. Examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl-  
25 pyrrolidone, etc. Examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, sodium carboxymethyl starch, etc. Examples of the solvent include water for injection, alcohol, propyleneglycol, macrogol, sesame oil, corn oil, etc. Examples of the solubilizer  
30 include polyethyleneglycol, propyleneglycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc. Examples of the suspending agent include surfactants such  
35 as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride,

benzetonium chloride, glycerin monostearate, etc.;  
hydrophilic polymers such as polyvinylalcohol,  
polyvinylpyrrolidone, sodium carboxymethyl cellulose,  
methyl cellulose, hydroxymethyl cellulose, hydroxyethyl  
5 cellulose, hydroxypropyl cellulose, etc.; etc. Examples of  
the isotonizing agent include sodium chloride, glycerin,  
D-mannitol, etc. Examples of the buffer include a buffer  
solution of phosphate, acetate, carbonate, citrate, etc.  
Examples of the soothing agent include benzylalcohol, etc.  
10 Examples of the preservative include paraoxybenzoic acid  
esters, chlorobutanol, benzylalcohol, phenethylalcohol,  
dehydroacetic acid, sorbic acid, etc. Examples of the  
antioxidant include sulfites, ascorbic acid, etc.

The present invention further provides with production  
15 methods of the compound of the formula (I) or a salt thereof.

The compound of the formula (I) or a salt thereof can  
be produced in accordance with per se known methods, for  
example, the methods described below, the methods described  
20 in JP-A-73476/1996, or analogous methods thereto, etc.

A salt of the compound of the formulas (II), (II'),  
(III), (IV), (V), (I-1), (I-2), (I-3) and (I-4) may be  
similar to that of the compound the formula (I).

In the following reaction steps, when the starting  
25 compounds have, as substituents, an amino group, a carboxyl  
group and/or hydroxy group, these groups may be protected  
by ordinary protective groups such as those generally  
employed in peptide chemistry, etc. After the reaction, if  
necessary, the protective groups may be removed to obtain  
30 the desired compound.

Examples of the amino-protective group include an  
optionally substituted C<sub>1-6</sub> alkylcarbonyl (e.g. acetyl,  
propionyl, etc.), formyl, phenylcarbonyl, C<sub>1-6</sub>  
alkyloxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl,  
35 t-butoxycarbonyl, etc.), aryloxycarbonyl (e.g.  
phenoxycarbonyl, etc.), C<sub>7-10</sub> aralkyloxycarbonyl (e.g.

benzyloxycarbonyl, etc.), trityl, phthaloyl, etc. These protective groups may be substituted by 1 to 3 substituents such as halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C<sub>1-6</sub> alkylcarbonyl (e.g. acetyl, propionyl, butyryl, etc.), nitro group, etc.

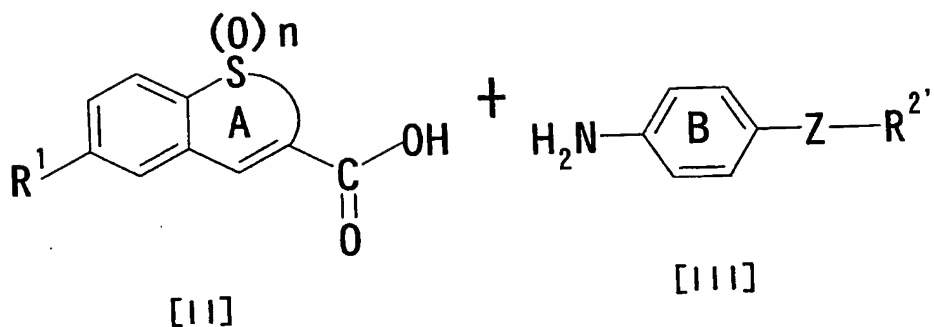
Examples of the carboxyl-protective group include an optionally substituted C<sub>1-6</sub> alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, silyl, etc. These protective groups may be substituted by 1 to 3 substituents such as halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C<sub>1-6</sub> alkylcarbonyl (e.g. acetyl, propionyl, butyryl, etc.), formyl, nitro group, etc.

Examples of the hydroxy-protective group include an optionally substituted C<sub>1-6</sub> alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C<sub>7-10</sub> aralkyl (e.g. benzyl, etc.), C<sub>1-6</sub> alkylcarbonyl (e.g. acetyl, propionyl, etc.), formyl, phenyloxycarbonyl, C<sub>7-10</sub> aralkyloxycarbonyl (e.g. benzyloxycarbonyl, etc.), pyranyl, furanyl, silyl, etc. These protective groups may be substituted by 1 to 4 substituents such as halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C<sub>1-6</sub> alkyl, phenyl, C<sub>7-10</sub> aralkyl, nitro group, etc.

These protective group may be introduced or removed by per se known methods (e.g. a method described in Protective Groups in Organic Chemistry (J. F. W. McOmie et al.; Plenum Press Inc.) or the methods analogous thereto.

For example, employable method for removing the protective groups is a method using an acid, a base, reduction, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.

[Method A]



wherein each symbol is as defined above.

This production method is carried out by reacting the  
 5 compound [II], a salt or a reactive derivative thereof with  
 the aniline derivative [III] or a salt thereof to obtain  
 the anilide Compound [I-1].

The condensation reaction of the compounds [II] and  
 [III] is carried out by usual methods for peptide synthesis.  
 10 Said methods for peptide synthesis are employed according  
 to optional known methods, for example, methods described  
 in "Peptide Synthesis" written by M. Bodansky and M. A.  
 Ondetti, Interscience, New York, 1966; "The Proteins",  
 volume 2, written by F. M. Finn and K. Hofmann, H. Nenrath  
 15 and R. L. Hill edition, Academic Press Inc., New York, 1976;  
 "peputido-gosei no kiso to jikken (Basis and Experiment of  
 Peptide Synthesis)" written by Nobuo Izumiya et al., Maruzen  
 K.K., 1985; etc., as well as azide method, chloride method,  
 acid anhydride method, mixed acid anhydride method, DCC

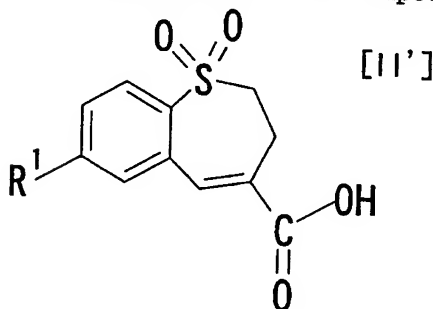
method, active ester method, method using Woodward reagent K, carbonyldiimidazole method, oxidation-reduction method, DCC/HONB method, etc. and in addition WSC method, method using diethyl cyanophosphate (DEPC), etc.

5       The condensation reaction can be carried out in a solvent. Examples of the solvents to be employed in the reaction include anhydrous or hydrous N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO),  
10       pyridine, chloroform, dichloromethane, tetrahydrofuran (THF), dioxane, acetonitrile, or a suitable mixture of these solvents.

      Usually, about 1-2 moles of the Compound [III] are used per 1 mole of the Compound [II]. The reaction temperature is generally about -20°C to about 50°C, preferably about  
15       -10°C to about 30°C and the reaction time is generally about 1 to about 100 hours, preferably about 2 to about 40 hours.

      The thus obtained anilide derivative [I-1] can be isolated and purified by known separation and purification  
20       methods such as concentration, concentration under reduced pressure, extraction, crystallization, recrystallization, solvent convert, chromatography, etc.

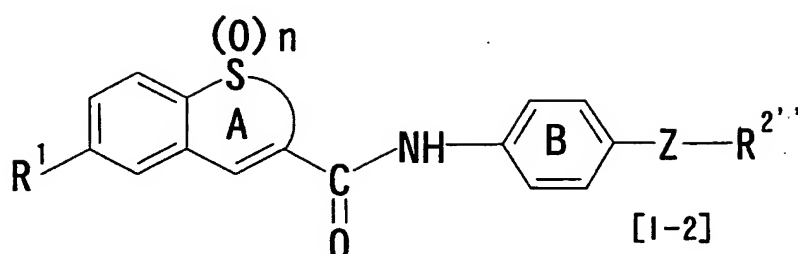
      In addition, the compound of the formula (II'):



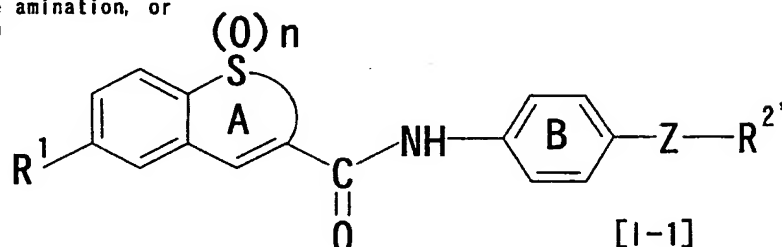
25       wherein R<sup>1</sup> is as defined above or a salt thereof is a novel compound and useful as an intermediate for producing the compound of the formula (I) or a salt thereof.

[Method B]





- ① ammoniumation  
 ② tertiary amination  
 ③ reductive amination, or  
 ④ oxidation



① When the group  $R^{2'}$  in Compound [I-2] is, for example, a tertiary amine residue, Compound [I-1] wherein the group  $R^{2'}$  is a quaternary ammonium can be produced by reacting Compound [I-2] with halogenated alkyl or halogenated aralkyl. Examples of the halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 5 moles of the halogenated alkyl (e.g. halogenated lower ( $C_{1-6}$ ) alkyl, etc.) or halogenated aralkyl (e.g. halogenated lower ( $C_{1-4}$ ) alkyl-phenyl, etc.) is used per mole of Compound [I-2]. The reaction is carried out in an inert solvent such as toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethylacetamide, etc., or a suitable mixture of these solvents. The reaction temperature is generally about  $10^{\circ}\text{C}$  to about  $160^{\circ}\text{C}$ , preferably about  $20^{\circ}\text{C}$  to about  $120^{\circ}\text{C}$  and the reaction time is generally about 1 hour to about 100 hours, preferably about 2 hours to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

② When the group  $R^{2'}$  in Compound [I-2] is, for example, a

secondary amine residue, Compound [I-1] wherein the group R<sup>2'</sup> is a tertiary amino can be produced by reacting Compound [I-2] with halogenated alkyl or halogenated aralkyl.

Examples of a halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 2 moles of the halogenated alkyl or halogenated aralkyl is used per mole of Compound [I-2]. If necessary, the reaction smoothly proceeds by addition of about once to thrice moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc.

This tertiary amination reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethylether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethylsulfoxide (DMSO), pyridine, etc., or a suitable mixture of these solvents.

The reaction temperature is generally about 0°C to 180°C, and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

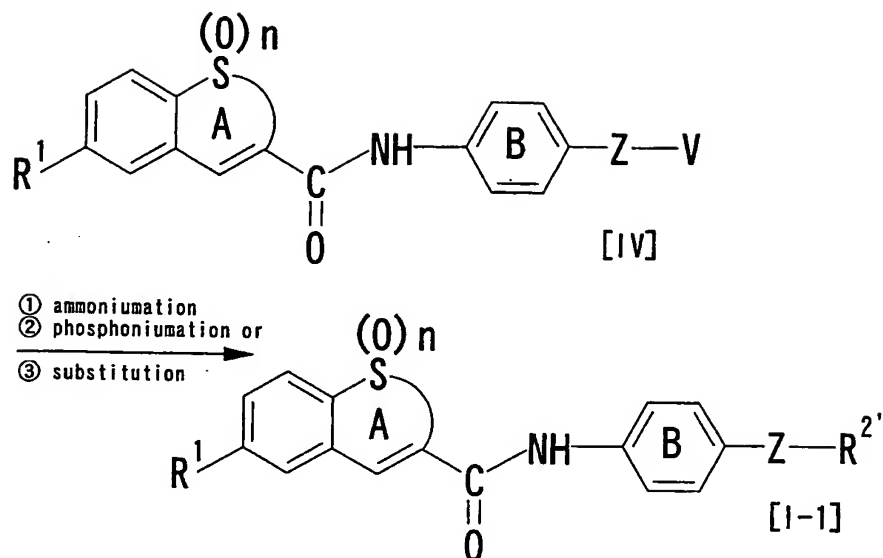
③ When the group R<sup>2''</sup> in Compound [I-2] is, for example, a secondary amine residue, Compound [I-1] wherein the group R<sup>2'</sup> is a tertiary amino can be produced by reacting Compound [I-2] with aldehyde compound in the presence of a reductive amination reagent such as triacetoxysodium boron hydride, cyanosodium boron hydride, sodium boron hydride, etc.

The conditions of this reductive amination reaction varies depending on the reagent to be used. For example, when triacetoxysodium boron hydride is used, reaction is carried out in an inert solvent such as dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran, diethylether, dioxane, acetonitrile, dimethylformamide (DMF), etc., or a suitable mixture of these solvents. In

this case, about 1 to 2 moles of the reagent is used per mole of Compound [I-2]. The reaction temperature is generally about 0°C to about 80°C, and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

④ When the group R<sup>2</sup> in Compound [I-2] is, for example, a sulfide residue or a tertiary amine residue, Compound [I-1] wherein the group R<sup>2</sup> is a sulfinyl group, a sulfonyl group or an amine oxide group can be produced by reacting Compound [I-2] with an oxidizing agent such as m-chloroperbenzoic acid (m-CPBA), perbenzoic acid, p-nitroperbenzoic acid, magnesium monoperoxyphthalate, peracetic acid, hydrogen peroxide, sodium periodate, potassium periodate, etc. The conditions of this oxidation reaction varies depending on the oxidizing agent to be used. For example, when m-chloroperbenzoic acid is used, reaction is carried out in an inert solvent such as dichloromethane, chloroform, 1,2-dichloroethane, diethylether, tetrahydrofuran, acetone, ethyl acetate, etc., or a suitable mixture of these solvents. Usually, about 1-3 moles of oxidizing agent is used per mole of Compound [I-2]. The reaction temperature is generally about -50°C to about 100°C (preferably -25°C to 25°C), and the reaction time is generally about 1 hour to about 40 hours.

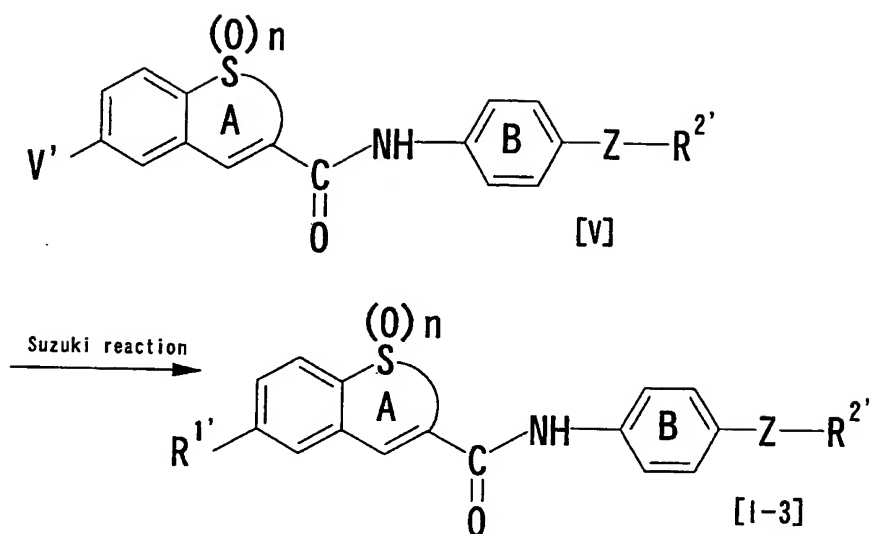
[Method C]



wherein V in the Compound [IV] is a halogen atom (chlorine, bromine, iodine, etc.), or a sulfonyloxy group (methanesulfonyloxy group, trifluoromethanesulfonyloxy group, benzenesulfonyloxy group, toluenesulfonyloxy group, etc.), and the other symbols are as defined above.

- ① Compound [I-1] wherein the group  $R^{2'}$  is a quaternary ammonium can be produced by reacting Compound [IV] and a tertiary amine. The reaction is carried out in an inert solvent such as toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethylacetamide, etc., or a suitable mixture of these solvents. Usually, about 1-3 moles of the tertiary amine is used per mole of Compound [IV]. The reaction temperature is generally about  $10^{\circ}\text{C}$  to about  $120^{\circ}\text{C}$ , and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.
- ② Compound [I-1] wherein the group  $R^{2'}$  is a quaternary phosphonium can be produced by reacting Compound [IV] and a tertiary phosphine. The reaction is carried out in an inert solvent such as toluene, benzene, xylene,

- dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, dimethylformamide (DMF), or a suitable mixture of these solvents. Usually, about 1-2 moles of the tertiary phosphine is used per mole of Compound [IV]. The reaction temperature is generally about 20°C to about 150°C, and the reaction time is generally about 1 hour to about 50 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.
- ③ Compound [I-1] wherein the group R<sup>2'</sup> is a secondary or tertiary amino group or a thio group can be produced by reacting Compound [IV] and primary or secondary amine compound or thiol compound. Usually, about 1 to 3 moles of the primary or secondary amine compound or the thiol compound is used per mole of Compound [IV]. If necessary, the reaction smoothly proceeds by addition of about once to thrice moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc. This substitution reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethylether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethylsulfoxide (DMSO), pyridine, etc., or a suitable mixture of these solvents. The reaction temperature is generally about -10°C to about 180°C, and the reaction time is generally about 1 hour to about 40 hours.
- The reaction is carried out preferably under inert gas (e.g. nitrogen, argon, etc.) atmosphere.
- [Method D]

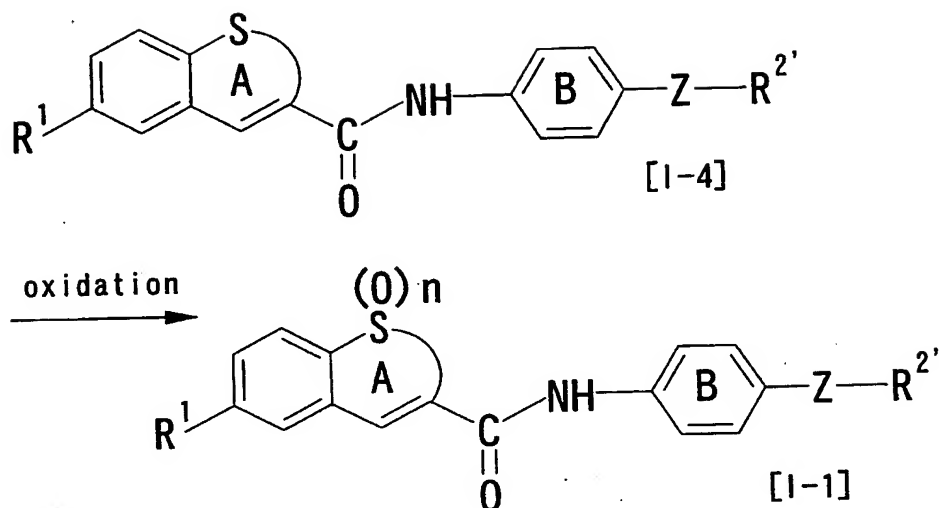


wherein V' is a halogen atom (bromine, iodine, etc.) or a sulfonyloxy group (trifluoromethanesulfonyloxy group, etc.), and the other symbols are as defined above.

5

Compound [I-3] wherein the group R<sup>1'</sup> is a 5- to 6-membered aromatic ring group can be produced by subjecting Compound [V] to, for example, Suzuki reaction [cross condensation reaction of aryl borate with e.g. aryl halide or aryloxytrifluoromethanesulfonate in the presence of palladium catalyst; A. Suzuki et al., Synth. Commun. 1981, 11, 513]. Usually, about 1-1.5 times moles of aryl borate is used per mole of Compound [V].

15 [Method E]



wherein each symbol is as defined above.

The Compound [I-1] can be produced by reacting the  
 5 Compound [I-4] with an oxidizing agent such as m-  
 chloroperbenzoic acid (m-CPBA), perbenzoic acid, p-  
 nitroperbenzoic acid, magnesium monoperoxyphthalate,  
 peracetic acid, hydrogen peroxide, sodium periodate,  
 10 potassium periodate, etc. The conditions of this oxidation  
 reaction varies depending on the oxidizing agent to be used.  
 For example, when m-chloroperbenzoic acid is used, reaction  
 is carried out in an inert solvent such as dichloromethane,  
 chloroform, 1,2-dichloroethane, diethylether,  
 tetrahydrofuran, acetone, ethyl acetate, etc., or a suitable  
 15 mixture of these solvents. Usually, about 1-3 moles of  
 oxidizing agent is used per mole of Compound [I-4]. The  
 reaction temperature is generally about -50°C to about 100°C  
 (preferably -25°C to 25°C), and the reaction time is  
 generally about 1 hour to about 40 hours.

20 The thus obtained anilide derivative [I-1] or [I-3]  
 can be isolated and purified by known separation and  
 purification methods such as concentration, concentration  
 under reduced pressure, extraction, crystallization,

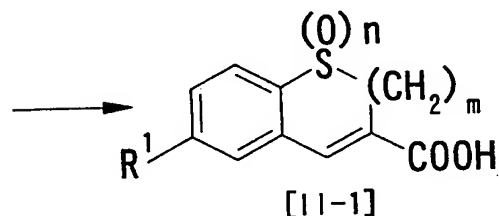
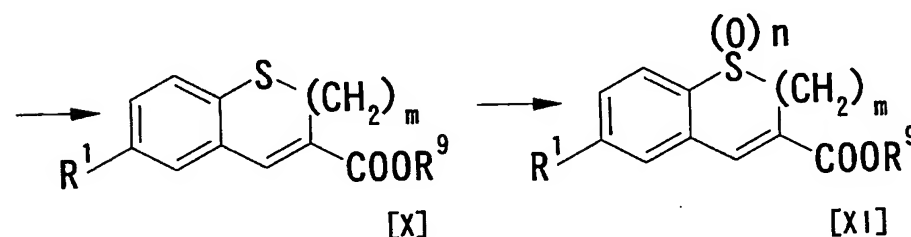
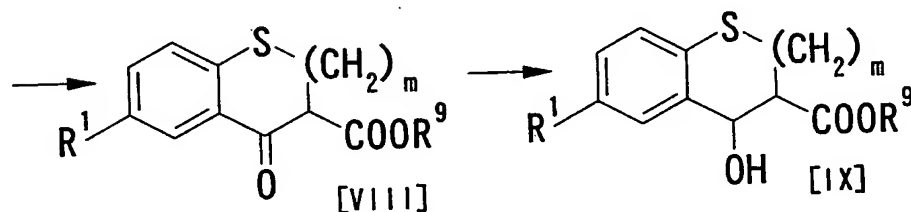
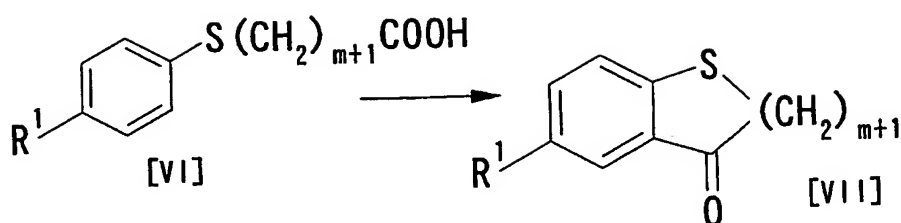
recrystallization, solvent convert, chromatography, etc.

Compound [II] used as a starting material can be produced by a known method (e.g. method described in JP-A-73476/1996, etc.) or the methods analogous thereto.

- 5 For example, Compound [II] can be produced by a method described in the following Reaction Scheme I or II, a method described in the following Reference Examples or the methods analogous thereto.

- 10 Reaction Scheme I



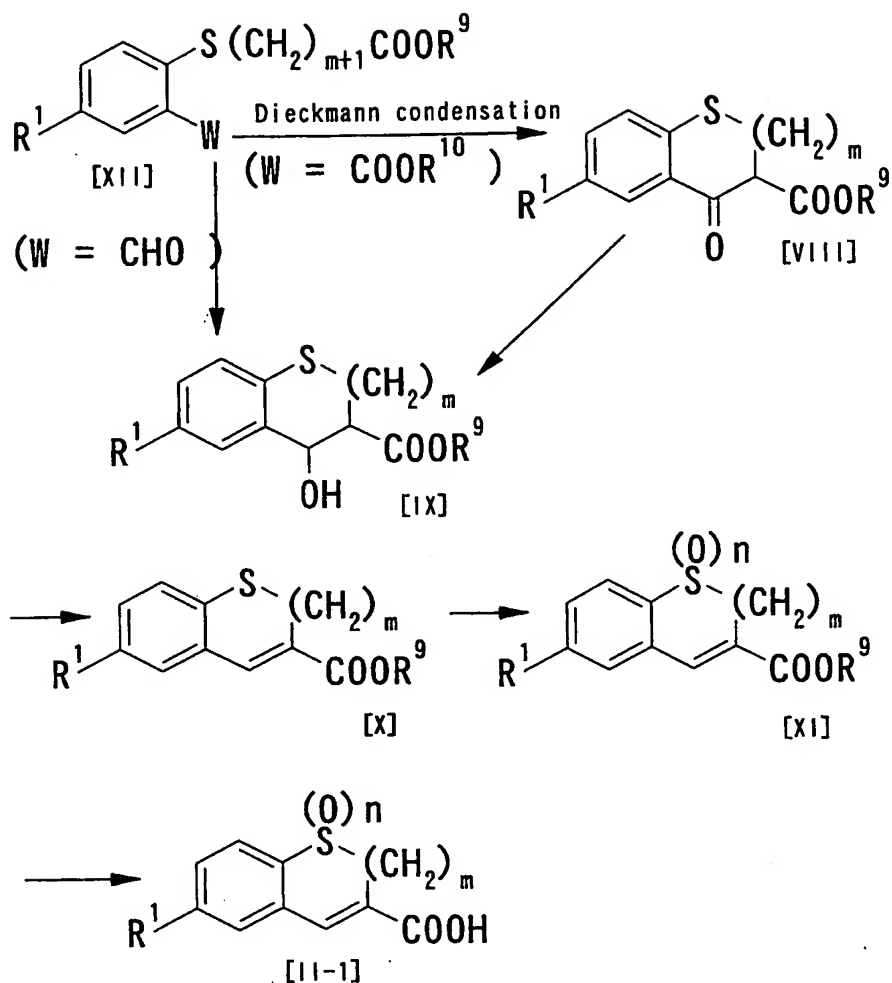


wherein R' is a C<sub>1-4</sub> alkyl group, m is an integer of 1 or 2, and the other symbols are as defined above.

- 5 In this reaction, the compound of the formula [VI] is heated with a polyphosphoric acid, or Compound [VI] is converted to acid chloride with thionyl chloride, oxalyl chloride, phosphorous oxychloride, phosphorous pentachloride, etc., followed by subjecting the resulting
- 10 acid chloride to usual Friedel-Crafts reaction and cyclizing

the same to produce Compound [VII]. Compound [VII] is reacted with carbonate ester in the presence of a base to produce ketoester [VIII]. Compound [VIII] is subjected to reduction with catalytic hydrogenation or sodium boron  
5 hydride, etc. to produce Compound [IX]. Compound [IX] is subjected to dehydration and ester hydrolysis by per se known method to produce Compound [X]. Compound [X] is converted to Compound [XI] with oxidation, and Compound [XI] is  
10 subjected to ester hydrolysis to produce unsaturated carboxylic acid [II-1].

Reaction Scheme II

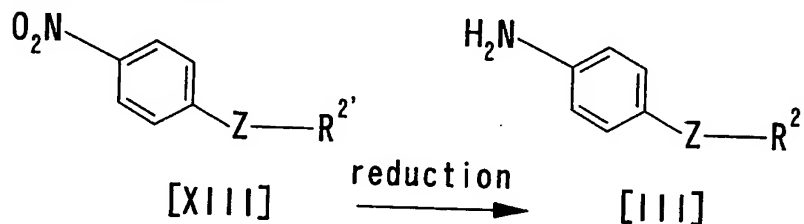


wherein  $R^{10}$  is a  $C_{1-4}$  alkyl group and the other symbols are as defined above.

- 5 The Compound [VIII] or [IX] can be produced by  
 10 subjecting the Compound [VII] to Dieckmann condensation  
 (J.P.Schaefer and J. J. Bloomfield, Org. Reactions, 1967,  
 15, 1). Compound [VIII] or [IX] is subjected to the  
 reactions as described in Reaction Scheme I to produce  
 10 unsaturated carboxylic acid [II-1].

Compound [III] can be produced by a known method (e.g. method described in JP-A-73476/1996, etc.) or the methods analogous thereto. For example, Compound [III] can be produced by a method described in the following Reaction Scheme III, a method described in the following Reference Examples or the methods analogous thereto.

Reaction Scheme III



The reduction of Compound [XIII] can be carried out per se known methods, for example, reduction with metal, reduction with metal hydride, reduction with metal hydride complex compound, reduction with diborane or substituted borane, catalytic hydrogenation, etc. That is, this reaction is carried out by treating Compound [XIII] with reduction agent. Examples of the reduction agent include metal such as reduced iron, zinc powder, etc.; alkali metal boron hydride (e.g. sodium boron hydride, lithium boron hydride, etc.); metal hydride complex compound such as aluminum lithium hydride, etc.; metal hydride such as sodium hydride etc.; organic tin compound (triphenyltin hydride, etc.), metal complex compound and metal salt such as nickel compound, zinc compound etc.; catalytic reduction agent using hydrogen and transit metal catalyst such as palladium, platinum, rhodium, etc.; diborane; etc. Among others, as the reduction agent, catalytic reduction agent using hydrogen and transit metal catalyst such as palladium, platinum, rhodium, etc.; reduced iron, etc. are preferable. The reaction is carried out in a solvent which does not affect the reaction. Examples of the solvent include benzene, toluene, xylene, chloroform, carbon tetrachloride,

dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, diethylether, tetrahydrofuran, dioxane, methanol, ethanol, propanol, isopropanol, 2-methoxyethanol, N,N-dimethylformamide, acetic acid, or a suitable mixture  
5 of these solvents, etc. The solvent is appropriately selected depending on kind of the reduction agent. The reaction temperature is generally about -20°C to about 150°C, preferably about 0°C to about 100°C, and the reaction time is generally about 1 to about 24 hours.

10 The resulting Compound [III] can be separated and purified with know separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, was recrystallized with, solvent conversion, chromatography, etc.

15

The compound of the formula (I) or a salt thereof of the present invention may be used in combination with other drug for the treatment or prevention of infectious disease of HIV (in particular, a pharmaceutical composition for the  
20 treatment or prevention of AIDS). In this case, these drugs can be formulated by mixing individually or simultaneously with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, which can be administered orally or non-orally as a pharmaceutical composition for  
25 the treatment or prevention of infectious disease of HIV.

In the case of formulating these effective components individually, while the individually formulated agents can be administered in the form of their mixture prepared by using e.g. a diluent when administered, the individually  
30 formulated agents can also be administered separately or simultaneously or with time intervals to the one and same subject. A kit for administering the individually formulated effective components in the form of their mixture prepared by using e.g. a diluent when administered (e.g.  
35 a kit for injection which comprises two or more ampoules each comprising a powdery component and a diluent for mixing

and dissolving two or more components when administered, etc.), a kit for administering the individually formulated agents simultaneously or with time intervals to the one and the same subject (e.g. a kit for tablets to be administered simultaneously or with time intervals, characterized by having two or more tablets each comprising an agent and said tablets being put in one or separate bags and, if necessary, a column to describe time to be administered each agent, etc.), etc. are also included by the pharmaceutical composition of the present invention.

Example of the other pharmaceutical agent for the treatment or prevention of infectious disease of HIV to be used in combination with the compound of the formula (I) or a salt thereof of the present invention include nucleotide reverse transcriptases inhibitor such as zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, adefovir, adefovir dipivoxil, fozivudine tidoxil, etc.; non-nucleotide reverse transcriptases inhibitor (including an agent having anti-oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, etc.; protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, palinavir, lasinavir, etc.; etc.

As the nucleotide reverse transcriptase inhibitor, zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, etc. are preferable; as the non-nucleotide reverse transcriptase inhibitor, nevirapine, delavirdine, efavirenz, etc. are preferable; and as the protease inhibitor, saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, etc. are preferable.

The compound of the formula (I) or a salt thereof of the present invention may be used in combination with, for example, CXCR4 antagonist (CXCR4 being a second receptor of T cell-tropic HIV-1) such as AMD-3100, etc., antibody against HIV-1 surface antigen, HIV-1 vaccine, etc., in addition to the above-mentioned protease inhibitor, reverse

transcriptase inhibitor, etc.

The compound of the formula (I) or a salt thereof of the present invention has potent CCR antagonistic activity (in particular, potent CCR5 antagonistic activity) and therefore can be used for the treatment or prevention of various infectious diseases of HIV, for example, AIDS in human. The compound of the formula (I) or a salt thereof of the present invention is low toxic and safely used as CCR5 antagonist for the treatment or prevention of AIDS and also for the prevention of the progression of AIDS.

The dose per day of the compound of the formula (I) or a salt thereof varies depending on the condition and body weight of a patient, administration route, etc. Typical daily dose per adult patient (body weight: 50Kg) for oral administration is about 5-1000mg, preferably about 10-600mg, more preferably about 10-300mg, and in particular about 15-150mg, as active ingredient [the compound of the formula (I) or a salt thereof] and the compound of the formula (I) or a salt thereof is administered once or 2-3 times par day.

20

When the compound of the formula (I) or a salt thereof is used in combination with a reverse transcriptase inhibitor and/or a protease inhibitor, the dose of the reverse transcriptase inhibitor or the protease inhibitor ranges, for example, from about 1/200-1/2 or more of usual dose to about 2-3 times or less of usual dose. In case that two or more drugs are used in combination, each dose of the drugs is appropriately adjusted if one drug affects metabolism of the other drug, while each dose of the drugs when they are used in combination is generally the same as the dose when they are used alone.

30

Typical daily dose of the reverse transcriptase inhibitor and the protease inhibitor is as follows:

zidovudine	: 100mg
35 didanosine	: 125-200mg
zalcitabine	: 0.75mg

lamivudine : 150mg  
stavudine : 30-40mg  
saquinavir : 600mg  
ritonavi : 600mg  
5 indinavir : 800mg  
nelfinavir : 750mg

In case of combination use of the compound of the formula (I) or a salt thereof with a reverse transcriptase inhibitor and/or a protease inhibitor preferred embodiments are shown below.

① A drug containing about 10-300mg of the compound of the formula (I) or a salt thereof and a drug containing about 50-200mg of zidovudine to one adult patient (body weight: 50Kg) are administered. Each of the drugs may be administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

② A drug containing about 10-300mg of the compound of the formula (I) or a salt thereof and a drug containing about 300-1200mg of saquinavir to one adult patient (body weight: 50Kg) are administered. Each of the drugs may be administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

#### Best Mode for Carrying out the Invention

The present invention is hereinafter described in more detail by means of the following Test Example, Formulation Example, Reference Example and Working Example, which are mere examples of the present invention and are not construed as limitative to the present invention.

The following gene manipulation is carried out in accordance with methods described in textbook (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or protocol attached to reagents.

#### Test Example

(1) Cloning of human CCR5 chemokine receptor

Cloning of CCR5 gene was carried out by PCR (polymerase chain



- reaction) from human spleen cDNA. With using 0.5ng of spleen cDNA (Toyobo, QUICK-Clone cDNA) as template, PCR was performed in DNA Thermal Cycler 480 (Perkin-Elmer) (reaction conditions: 30 cycles of 95°C for 1 minute, 60°C for 1 minute, and 75°C for 5 minutes) by adding primer set,
- 5'-CAGGATCCGATGGATTATCAAGTGTCAAGTCCAA-3' (25pmol) and 5'-TCTAGATCACAAGCCCACAGATATTTCTGCTCC-3' (25pmol), which were designed referring to nucleotide sequence of CCR5 gene reported by Samson et al. (Biochemistry, 35(11), 3362-3367 (1996)) and by using TaKaRa EX Taq (Takara Shuzo).
- The resultant PCR product was subjected to agarose gel electrophoresis to collect about 1.0kb DNA fragment, which was subjected to Original TA Cloning Kit (Funakoshi) to carry out cloning of CCR5 gene.
- (2) Preparation of plasmid for expression of human CCR5
- The plasmid obtained in the above (1) was digested with restriction enzymes XbaI (Takara Shuzo) and BamHI (Takara Shuzo) and subjected to agarose gel electrophoresis to collect about 1.0kb DNA fragment. The DNA fragment was mixed with plasmid pcDNA3.1 (Funakoshi) for expression in animal cells, said plasmid being digested with XbaI and BamHI, and they were ligated with DNA Ligation Kit Ver.2 (Takara Shuzo). The resulting plasmid was subjected to transformation of competent cell of E. coli JM109 (Takara Shuzo) to obtain plasmid pCKR5.
- (3) Introduction of plasmid for expression of human CCR5 into CHO-K1 cell and Expression of said plasmid in CHO-K1 cell
- CHO-K1 cells were grown in 750ml of tissue culture flask (Becton Dickinson) using Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum (Life Tech Oriental) and took off with 0.5g/L trypsin-0.2g/L EDTA (Life Tech Oriental). The cells were washed with PBS (Life Tech Oriental), centrifuged (1000rpm, 5 minutes), and suspended in PBS. With using Gene Pulser (Bio-Rad Laboratories), DNA was introduced into the cells under the conditions shown

below. That is, to the cuvette of 0.4cm gap were added  $8 \times 10^6$  cells and  $10 \mu\text{g}$  of plasmid pCCR5 for expression of human CCR5, and electroporation was carried out under 0.25kV of voltage and  $960 \mu\text{F}$  of capacitance. The cells were

5 transferred into Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum, and cultivated for 24 hours. The cells were again took off and centrifuged, and suspended in Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum and  $500 \mu\text{g/ml}$  of geneticin (Life Tech

10 Oriental). The suspension was diluted to give  $10^4$  cells/ml of the suspension, which was inoculated on 96 well plate (Becton Dickinson) to give geneticin resistant cells. The resulting geneticin resistant cells were cultivated in 96 well plate (Becton Dickinson), and cells expressing CCR5

15 were selected from the geneticin resistant cells. That is, in assay buffer (Ham's F12 medium containing 0.5% BSA and 20mM HEPES (Wako Pure Chemical, pH7.2) to which was added 200pM of [ $^{125}\text{I}$ ]-RANTES (Amersham) as ligand, binding reaction was carried out at room temperature for 40 minutes, and the

20 buffer was washed with cooled PBS. To the buffer was added  $50 \mu\text{l/well}$  of 1M NaOH, and the mixture was stirred. Radioactivity was determined with  $\gamma$ -counter to select CHO/CCR5 cells which specifically bind to the ligand.

25 (4) Evaluation of Test Compounds based on CCR5 antagonistic activity

The CHO/CCR5 were inoculated on 96 well microplate ( $5 \times 10^4$  cells/well) and cultivated for 24 hours. The medium was removed by means of suction, and to each well was added assay buffer containing Test Compound ( $1 \mu\text{M}$ ) and then 100pM

30 of [ $^{125}\text{I}$ ]-RANTES (Amersham) as ligand. Binding assay was carried out at room temperature for 40 minutes, and assay buffer was removed by means of suction. Each well was washed twice with cooled PBS, and  $200 \mu\text{l}$  of Microscint-20 (Packard Instrument, Inc.) was added to each well. Radio-activity

35 was determined with Top-Count Micro Scintillation Counter (Packard Instrument, Inc.).

According to the method described above, inhibition rate of Test Compound (whose number is referred to in the following Examples) to CCR5 binding.

The results are shown in Table 1.

5 Table 1

	<u>Compound Number</u>	<u>Inhibition Rate (%)</u>
	4	91
	27	100
10	29	100
	30	99
	44	96
	54	99
	73	94
15	74	94
	75	95
	84	97
	97	92
	98	98
20	111	95
	123	94
	124	97
	125	92
	129	95

25

(5) Inhibitory effect on HIV-1 infection to MAGI-CCR5 cell

The plasmid where  $\beta$ -galactosidase gene was ligated downstream of HIV-1 LTR was introduced into CD4 positive HeLa cell, to which human CCR5 was further introduced to obtain transformant MAGI-CCR5. By using said transformant MAGI-CCR5, degree of HIV-1 infection was calculated from  $\beta$ -galactosidase activity (blue color due to decomposition of 5-bromo-4-chloro-3-indolyl- $\beta$ -D-galactopyranoside). Specifically, MAGI-CCR5 cells were suspended in DMEM medium containing 10% serum to prepare  $5 \times 10^4$  cells/ml suspension. To each well of 96 well plate was inoculated 200  $\mu$ l of the

30

35

suspension, and the cells were cultivated at 37°C overnight. The medium was removed by means of suction, and to the residue was added 100  $\mu$ l of the above medium containing 1.6  $\mu$ M of Test Compound and 100  $\mu$ l of the above medium containing  
5 300PFU of HIV-1 BA-L cells. The cells were cultivated at 37°C for 2 days. The medium was removed by means of suction. To the residue was added 200  $\mu$ l of cell fixative (PBS containing 1% formaldehyde and 0.2% glutaraldehyde), and the mixture was allowed to stand at room temperature for  
10 5 minutes and washed twice with PBS. To the mixture was added 100  $\mu$ l of staining solution (PBS containing 4  $\mu$ M potassium ferrocyanide, 4  $\mu$ M potassium ferricyanide, 2  $\mu$ M MgCl<sub>2</sub>, and 0.4mg/ml X-gal), and the mixture was allowed to stand at 37°C for 50 minutes and washed twice with PBS. The number  
15 of blue cells was counted by microscope and defined as the number of cells infected with HIV-1. According to this method, inhibition rate on HIV-1 infection was determined. The results are shown in Table 2.

20 Table 2

	Compound No.	Inhibition Rate (%)
	30	91
25	29	91
	97	87
	98	91

The pharmaceutical composition for antagonizing CCR5  
30 (e.g. a medicament for the treatment or prevention of infectious disease of HIV, a medicament for the treatment or prevention of AIDS, etc.) comprising the compound of the formula (I) or a salt thereof of the present invention, as an active ingredient, can be prepared, for example, by the  
35 following prescriptions:  
1. Capsule

- (1) Compound obtained in Working Example 4 40mg  
(2) lactose 70mg  
(3) fine crystalline cellulose 9mg  
(4) magnesium stearate 1mg  
5 1 capsule 120mg  
(1), (2), (3) and 1/2 of (4) are mixed and then granulated.  
To the granules is added the remainder of (4), and the whole  
is filled into a gelatin capsule.
2. Tablet
- 10 (1) Compound obtained in Working Example 4 40mg  
(2) lactose 58mg  
(3) corn starch 18mg  
(4) fine crystalline cellulose 3.5mg  
(5) magnesium stearate 0.5mg  
15 1 tablet 120mg  
(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then  
granulated. To the granules are added the remainders of (4)  
and (5), followed by subjecting the mixture to compression  
molding.
- 20 3. Capsule  
(1) Compound obtained in Working Example 115 40mg  
(2) lactose 70mg  
(3) fine crystalline cellulose 9mg  
(4) magnesium stearate 1mg  
25 1 capsule 120mg  
(1), (2), (3) and 1/2 of (4) are mixed and then granulated.  
To the granules is added the remainder of (4), and the whole  
is filled into a gelatin capsule.
4. Tablet
- 30 (1) Compound obtained in Working Example 115 40mg  
(2) lactose 58mg  
(3) corn starch 18mg  
(4) fine crystalline cellulose 3.5mg  
(5) magnesium stearate 0.5mg  
35 1 tablet 120mg  
(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed and then

granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the mixture to compression molding.

## 5 Working Example

### Working Example 1 (Production of Compound 1)

To a solution of 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (177mg; purity: about 50%) and 1-hydroxybenzotriazole (HOBt) (90mg) in DMF (5ml) was added at room temperature 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSC) (127mg), and the mixture was stirred for 1 hour. To the mixture were added a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (107mg) and triethylamine (0.12ml) in DMF (5ml) and a piece of 4-dimethylaminopyridine, and the mixture was stirred for 64 hours. The mixture was concentrated under reduced pressure, and to the residue was added water. The mixture was extracted with dichloromethane, and the organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:1) and recrystallized from ethanol/diethylether to give yellow crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 1) (31.6mg).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.38-1.84 (4H, m), 2.23 (3H, s), 2.58-2.80 (1H, m), 3.10-3.45 (8H, m), 3.61 (2H, s), 3.67-3.78 (2H, m), 3.83-3.94 (4H, m), 3.99-4.09 (2H, m), 7.00 (2H, d, J=8.8 Hz), 7.19-7.38 (3H, m), 7.49-7.60 (4H, m), 7.62-7.71 (2H, m), 7.89-7.95 (1H, m), 8.19 (1H, d, J=8.4 Hz).  
IR (KBr) 3277, 1659, 1603, 1522, 1313, 1234, 1124, 928, 820 cm<sup>-1</sup>

### 35 Working Example 2 (Production of Compound 2)

To a solution of N-[4-[N-methyl-N-

(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (36mg) in ethanol/methanol (10/5ml) was added at room temperature concentrated hydrochloric acid (0.5ml), and the mixture was stirred for a few minutes. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. To the residue was added diethylether, and precipitated solid was collected by filtration, which was washed with diethylether to give yellow powder of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide dihydrochloride (Compound 2) (34mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.65-2.18 (4H, m), 2.60 (3H, s), 3.01-3.12 (2H, m), 3.16-3.51 (7H, m), 3.62-3.87 (6H, m), 3.93-4.07 (2H, m), 4.10-4.22 (1H, m), 4.39-4.51 (1H, m), 7.08 (2H, d, J=8.8 Hz), 7.53-7.58 (3H, m), 7.72 (2H, d, J=8.8 Hz), 7.80-7.92 (3H, m), 8.02-8.10 (2H, m), 10.42 (1H, br s).

#### Working Example 3 (Production of Compound 3)

To a solution of 7-(4-methoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) in THF (10ml) were added at room temperature oxalyl chloride (0.2ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (20ml). To the solution were added dropwise at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (107mg) and triethylamine (0.12ml), and the mixture was stirred at room temperature for 4 hours. The mixture was added to vigorously stirred water to stop the reaction, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography

- (ethanol/ethyl acetate=1:2) and recrystallized from ethanol to give colorless crystals of 7-(4-methoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 3) (161.1mg).
- 5 m.p. 247-249 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.68-1.83 (4H, m), 2.21 (3H, s), 2.52-2.74 (1H, m), 3.16 (2H, d, J=6.6 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 3.87 (3H, s), 3.98-4.10
- 10 (2H, m), 7.02 (2H, d, J=8.8 Hz), 7.30-7.35 (3H, m), 7.52-7.57 (4H, m), 7.62-7.70 (2H, m), 7.91 (1H, br s), 8.20 (1H, d, J=8.0 Hz).
- IR (KBr) 3246, 1655, 1633, 1605, 1518, 1410, 1317, 1294, 1250, 1171, 1128, 825 cm<sup>-1</sup>
- 15 Anal. for C<sub>31</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>S
- Calcd. C, 70.56 ; H, 6.97 ; N, 7.26
- Found. C, 70.43 ; H, 6.83 ; N, 7.22.
- Working Example 4 (Production of Compound 4)
- To a suspension of 7-(4-ethoxyphenyl)-1,1-dioxo-
- 20 2,3-dihydro-1-benzothiepine-4-carboxylic acid (16.90g) in THF (340ml) and DMF (2ml) was added at room temperature thionyl chloride (3.62ml), and the mixture was stirred for 2 hours. The mixture was added at room temperature to a suspension of 4-[N-methyl-N-(tetrahydropyran-4-
- 25 yl)aminomethyl]aniline 2hydrochloride (15.21g) and triethylamine (40ml) in THF (150ml) for 1 hour, and the mixture was stirred for 4 hours. The mixture was concentrated under reduced pressure, and precipitated colorless crystals were collected by filtration, which were
- 30 washed with water, ethanoethyl acetate and diisopropylether to give crude crystals (21.90g). The crude crystals were purified with recrystallization from THF/ethanol to give colorless crystals of 7-(4-
- 35 ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 4) (21.02g).



m.p. 243-246 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45 (3H, t, J=7.0 Hz), 1.67-1.80 (4H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.13-3.20 (2H, m), 3.28-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 3.97-4.08 (2H, m), 4.10 (2H, q, J=7.0 Hz), 7.06 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.52-7.57 (4H, m), 7.63-7.70 (2H, m), 7.89 (1H, br s), 8.20 (1H, d, J=8.0 Hz).

IR (KBr) 3428, 1657, 1635, 1603, 1518, 1410, 1317, 1294, 1246, 1128, 827 cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 68.55 ; H, 6.47 ; N, 5.00

Found. C, 68.68 ; H, 6.50 ; N, 4.92.

Working Example 5 (Production of Compound 4)

To a solution of 7-(4-ethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) in THF (10ml) were added at room temperature oxalyl chloride (0.18ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (20ml). To the solution were added dropwise at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (102mg) and triethylamine (0.12ml), and the mixture was stirred at room temperature for 4 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:2) and recrystallized from ethanol to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 4) (134mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45 (3H, t, J=7.0 Hz), 1.67-1.80 (4H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.13-3.20 (2H, m), 3.28-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 3.97-4.08

(2H, m), 4.10 (2H, q, J=7.0 Hz), 7.06 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.52-7.57 (4H, m), 7.63-7.70 (2H, m), 7.89 (1H, br s), 8.20 (1H, d, J=8.0 Hz).

IR (KBr) 3428, 1657, 1635, 1603, 1518, 1410, 1317, 1294,  
5 1246, 1128, 827  $\text{cm}^{-1}$

Anal. for  $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$

Calcd. C, 68.55 ; H, 6.47 ; N, 5.00

Found. C, 68.16 ; H, 6.52 ; N, 5.13.

Working Example 6 (Production of Compound 5)

10 To a solution of 7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (2.5g) in THF (125ml) was added at room temperature 6N hydrochloric acid (1.5ml), and the mixture was stirred for 0.5 hour and  
15 concentrated under reduced pressure. To the mixture was added diethylether, colorless crystals were collected by filtration to give crude crystals (2.61g), which were purified with recrystallization from 90% ethanol to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
20 hydrochloride (Compound 5) (2.33g).

m.p. 255  $^{\circ}\text{C}$  (dec.)

$^1\text{H}$ -NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.45 (3H, t, J=7.0 Hz), 1.53-1.86 (2H, m), 1.93-2.21 (2H, m), 2.48 (3H, br s), 2.94-3.35 (5H, m), 3.70-3.76 (2H, m), 3.78-3.99 (3H, m), 4.10 (2H, q, J=7.0 Hz), 4.16-4.35 (1H, m), 7.00 (2H, d, J=8.8 Hz), 7.57-7.70 (5H, m), 7.87-7.92 (1H, m), 8.00-8.08 (3H, m), 8.18 (1H, d, J=8.4 Hz), 9.72-9.83 (1H, m).

30 Anal. for  $\text{C}_{32}\text{H}_{37}\text{N}_2\text{O}_5\text{SCl}\cdot 0.5\text{H}_2\text{O}$

Calcd. C, 63.40 ; H, 6.32 ; N, 4.62 ; Cl, 5.85

Found. C, 63.36 ; H, 6.10 ; N, 4.49 ; Cl, 5.76.

Working Example 7 (Production of Compound 6)

To a solution of 7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid  
35 (150mg) in THF (10ml) were added at room temperature oxalyl

chloride (0.07ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (20ml).

To the solution were added dropwise at 0°C 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (102mg) and triethylamine (0.12ml), and the mixture was stirred at room temperature for 16 hours. The mixture was added to vigorously stirred water to stop the reaction and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:2) and recrystallized from ethanol to give colorless crystals of 7-(3,4-methylenedioxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 6) (133mg).  
m.p. 245-248 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.66-1.83 (4H, m), 2.21 (3H, s), 2.52-2.74 (1H, m), 3.17 (2H, t, J=7.0 Hz), 3.29-3.45 (2H, m), 3.58 (2H, s), 3.70-3.76 (2H, m), 3.96-4.10 (2H, m), 6.05 (2H, s), 6.92 (1H, d, J=8.8 Hz), 7.07-7.12 (2H, m), 7.31-7.35 (3H, m), 7.52-7.67 (4H, m), 7.89 (1H, br s), 8.20 (1H, d, J=8.0 Hz).

IR (KBr) 3259, 1651, 1597, 1512, 1477, 1319, 1294, 1232, 1128, 1036, 930, 810 cm<sup>-1</sup>

Anal. for C<sub>31</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 66.41 ; H, 5.75 ; N, 5.00

Found. C, 66.34 ; H, 5.75 ; N, 4.85.

#### Working Example 8 (Production of Compound 7)

To a solution of 7-(4-chlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) in THF (10ml) were added at room temperature oxalyl chloride (0.08ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (15ml). The solution

- was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (104mg) and triethylamine (0.12ml) in THF (5ml), and the mixture was stirred at room temperature for 19 hours. To the mixture
- 5 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:2) and
- 10 recrystallized from ethanol/diisopropylether to give colorless crystals of 7-(4-chlorophenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 7) (154.8mg).
- 15 m.p. 247-250 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.62-1.85 (4H, m), 2.21 (3H, s), 2.52-2.73 (1H, m), 3.14-3.21 (2H, m), 3.29-3.44 (2H, m), 3.57 (2H, s), 3.69-3.76 (2H, m), 3.97-4.10 (2H, m), 7.31-7.35 (3H, m), 7.45-7.56 (6H, m), 7.63-7.72 (2H, m), 7.90 (1H, br s), 8.24 (1H, d, J=8.0 Hz).
- 20 IR (KBr) 3246, 1655, 1601, 1529, 1410, 1317, 1294, 1130, 818 cm<sup>-1</sup>
- Anal. for C<sub>30</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>SCl
- Calcd. C, 65.38 ; H, 5.67 ; N, 5.08
- 25 Found. C, 65.54 ; H, 5.56 ; N, 4.98.

Working Example 9 (Production of Compound 8)

- To a solution of 7-(4-fluorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) in THF (10ml) were added at room temperature oxalyl chloride
- 30 (0.08ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (15ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (109mg) and
- 35 triethylamine (0.13ml) in THF (5ml), and the mixture was stirred at room temperature for 24 hours. To the mixture

- was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethanol to give colorless crystals of 7-(4-fluorophenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 8) (128.5mg).
- 5  
10 m.p. 219-221 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.52-1.83 (4H, m), 2.21 (3H, s), 2.53-2.75 (1H, m), 3.14-3.21 (2H, m), 3.30-3.45 (2H, m), 3.58 (2H, s), 3.71-3.78 (2H, m), 3.99-4.10 (2H, m), 7.15-7.24 (2H, m), 7.31-7.35 (3H, m), 7.52-7.70 (6H, m), 7.95 (1H, br s), 8.23 (1H, d, J=8.6 Hz).
- 15 IR (KBr) 3273, 1655, 1601, 1516, 1410, 1311, 1128, 825 cm<sup>-1</sup>  
Anal. for C<sub>30</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>SF·0.5H<sub>2</sub>O  
Calcd. C, 66.28 ; H, 5.93 ; N, 5.15  
Found. C, 66.56 ; H, 5.90 ; N, 5.13.
- 20 Working Example 10 (Production of Compound 9)  
To a solution of 7-(4-trifluoromethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (10ml) were added at room temperature oxalyl chloride (0.8ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (10ml).  
The solution was added at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (114mg) and triethylamine (0.13ml) in THF (5ml), and the mixture was stirred at room temperature for 14 hours. To the mixture was added water, and the mixture was extracted with dichloromethane. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and precipitated crystals were recrystallized from ethanol to give colorless crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-
- 25  
30  
35

yl)aminomethyl]phenyl]-7-(4-trifluoromethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
(Compound 9) (208.9mg).

m.p. 270-272 °C

5 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.37-1.61 (2H, m), 1.63-1.78 (2H, m), 2.10 (3H, s), 2.46-2.67 (1H, m), 3.07-3.13 (2H, m), 3.18-3.35 (2H, m), 3.52 (2H, s), 3.75-3.96 (4H, m), 7.27 (2H, d, J=8.5 Hz), 7.56 (1H, s), 7.67 (2H, d, J=8.5 Hz),  
10 7.90 (2H, d, J=8.4 Hz), 7.97-8.06 (3H, m), 8.14-8.18 (2H, m).

IR (KBr) 3245, 1654, 1636, 1601, 1529, 1410, 1325, 1294, 1173, 1130, 1072, 827 cm<sup>-1</sup>

Anal. for C<sub>31</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>SF<sub>3</sub>

Calcd. C, 63.68 ; H, 5.34 ; N, 4.79

15 Found. C, 63.64 ; H, 5.30 ; N, 4.70.

Working Example 11 (Production of Compound 10)

To a solution of 7-(4-ethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (10ml) were added at room temperature oxalyl chloride  
20 (0.09ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (15ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (128mg) and  
25 triethylamine (0.15ml) in THF (5ml), and the mixture was stirred at room temperature for 64 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced  
30 pressure, and precipitated crystals were recrystallized from ethanol to give pale yellow crystals of 7-(4-ethylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 10) (173.6mg).  
35 m.p. 257-260 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.29 (3H, t, J=6.7 Hz), 1.56-1.83 (4H,

m), 2.21 (3H, s), 2.54-2.71 (1H, m), 2.72 (2H, q, J=6.7 Hz), 3.17 (2H, t, J=6.7 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.70-3.76 (2H, m), 3.98-4.11 (2H, m), 7.31-7.35 (5H, m), 7.54 (2H, d, J=8.0 Hz), 7.55 (2H, d, J=8.4 Hz), 7.66 (1H, s), 7.71 (1H, dd, J=8.4 Hz), 7.92 (1H, br s), 8.21 (1H, d, J=8.4 Hz).

IR (KBr) 3248, 1657, 1635, 1599, 1525, 1410, 1317, 1294, 1128, 824  $\text{cm}^{-1}$

Anal. for  $\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_4\text{S}$

10 Calcd. C, 70.56 ; H, 6.66 ; N, 5.14  
Found. C, 70.30 ; H, 6.73 ; N, 5.29.

Working Example 12 (Production of Compound 11)

To a solution of 7-(4-isopropylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in 15 THF (10ml) were added at room temperature oxalyl chloride (0.09ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (15ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (122mg) and 20 triethylamine (0.14ml) in THF (5ml), and the mixture was stirred at room temperature for 20 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, 25 dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethanol to give colorless crystals of 7-(4-isopropylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 11) (189.8mg, 67%).

m.p. 240-247 °C

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (6H, d, J=7.0 Hz), 1.52-1.83 (4H, m), 2.21 (3H, s), 2.55-2.77 (1H, m), 2.90-3.04 (1H, m), 3.17 (2H, t, J=6.6 Hz), 3.37 (2H, dt, J=2.8, 11.0 Hz), 3.58 (2H,

s), 3.70-3.76 (2H, m), 3.98-4.09 (2H, m), 7.31-7.38 (5H, m), 7.52-7.58 (4H, m), 7.66-7.73 (2H, m), 7.98 (1H, br s), 8.21 (1H, d, J=8.4 Hz).

IR (KBr) 3251, 1655, 1601, 1525, 1410, 1317, 1296, 1130, 821 cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>S

Calcd. C, 70.94 ; H, 6.86 ; N, 5.01

Found. C, 70.89 ; H, 6.61 ; N, 7.75.

Working Example 13 (Production of Compound 12)

To a solution of 7-(4-tert-butylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (10ml) were added at room temperature oxalyl chloride (0.09ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in tetrahydrofuran (15ml).

The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (119mg) and triethylamine (0.14ml) in THF (5ml), and the mixture was stirred at room temperature for 16 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and precipitated crystals were recrystallized from ethanol to give colorless crystals of 7-(4-tert-butylphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 12) (209.8mg).

m.p. 247-249 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.37 (9H, s), 1.52-1.83 (4H, m), 2.21 (3H, s), 2.54-2.74 (1H, m), 3.13-3.20 (2H, m), 3.29-3.45 (2H, m), 3.58 (2H, s), 3.68-3.79 (2H, m), 3.98-4.10 (2H, m), 7.31-7.35 (3H, m), 7.46-7.60 (6H, m), 7.66 (1H, d, J=1.8 Hz), 7.71 (1H, dd, J=8.0, 1.8 Hz), 7.99 (1H, br s), 8.21 (1H, d, J=8.0 Hz).

IR (KBr) 3278, 1655, 1599, 1512, 1313, 1300, 1130, 821 cm<sup>-1</sup>



Anal. for  $C_{34}H_{40}N_2O_4S \cdot 0.2H_2O$

Calcd. C, 70.85 ; H, 7.07 ; N, 4.86

Found. C, 70.60 ; H, 6.91 ; N, 4.78.

Working Example 14 (Production of Compound 13)

- 5 To a solution of 7-[4-(1-pyrrolidinyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (75mg) in DMF (5ml) was added at room temperature thionyl chloride (0.1ml), and the mixture was stirred for 1 hour.
- 10 The solvent was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (10ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (53mg) and triethylamine (0.5ml) in dichloromethane (5ml), and the mixture was stirred at room temperature for 16 hours.
- 15 To the mixture was added water, and the mixture was extracted with dichloromethane. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl
- 20 acetate=1:2) to give yellow crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(1-pyrrolidinyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 13) (36.3mg).
- 25  $^1H$ -NMR (200MHz, DMSO- $d_6$ )  $\delta$  1.42-1.67 (4H, m), 1.89-2.04 (4H, m), 2.10 (3H, s), 2.45-2.68 (1H, m), 2.98-3.10 (2H, m), 3.17-3.36 (6H, m), 3.52 (2H, s), 3.69-3.81 (2H, m), 3.83-3.96 (2H, m), 6.65 (2H, d, J=8.6 Hz), 7.27 (2H, d, J=8.0 Hz), 7.52 (1H, s), 7.61-7.71 (4H, m), 7.76-7.84 (1H, m), 7.98-8.02 (2H, m), 10.16 (1H, s).
- 30 IR (KBr) 3278, 1657, 1606, 1525, 1379, 1315, 1294, 1167, 1128, 812  $cm^{-1}$

Working Example 15 (Production of Compound 14)

- 35 To a solution of 7-(4-piperidinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg) in DMF (10ml) was added at room temperature thionyl chloride (0.1ml), and the mixture was stirred for 1 hour. The solvent

was evaporated under reduced pressure, and the residue was dissolved in dichloromethane (15ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (125mg) and triethylamine (0.5ml) in dichloromethane (5ml), and the mixture was stirred at room temperature for 16 hours. The mixture was added to water, and the mixture was extracted with dichloromethane. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:4) to give yellow crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-piperidinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 14) (39.5mg).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.39-1.77 (10H, m), 2.10 (3H, s), 2.46-2.70 (1H, m), 3.01-3.11 (2H, m), 3.17-3.35 (6H, m), 3.52 (2H, s), 3.72-3.81 (2H, m), 3.83-3.97 (2H, m), 7.05 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=8.4 Hz), 7.53 (1H, s), 7.67 (2H, d, J=8.4 Hz), 7.68 (2H, d, J=8.8 Hz), 7.84 (1H, dd, J=8.2, 2.2 Hz), 8.01-8.05 (2H, m), 10.17 (1H, s).  
IR (KBr) 3280, 1657, 1603, 1522, 1315, 1292, 1238, 1126, 818 cm<sup>-1</sup>

Working Example 16 (Production of Compound 15)

To a solution of 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid hydrochloride (200mg) and 1-hydroxybenzotriazole (0.12g) in DMF (5ml) was added at room temperature 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (0.18g), and the mixture was stirred for 1 hour. To the mixture was added a solution of 4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]aniline (0.19g) and triethylamine (0.2ml) in DMF (3ml), and the mixture was stirred for 64 hours. The mixture was concentrated under reduced pressure, and to the residue was added water. The mixture was extracted with ethyl acetate,

and the organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:1) to give

- 5 yellow crystals of N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 15) (119mg).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.51-1.75 (4H, m), 1.77-1.91 (4H, m),  
10 2.20 (3H, s), 2.44-2.65 (1H, m), 3.11-3.20 (2H, m), 3.23-3.28 (4H, m), 3.57 (2H, s), 3.69-3.75 (2H, m), 3.87-3.91 (4H, m), 3.95 (4H, s), 7.00 (2H, d, J=8.8 Hz), 7.30-7.35 (3H, m), 7.51-7.58 (4H, m), 7.64 (1H, br s), 7.65-7.73 (1H, m), 7.88-7.93 (1H, m), 8.18 (1H, d, J=7.6 Hz).  
15 IR (KBr) 3346, 1653, 1608, 1520, 1410, 1310, 1238, 1165, 1126, 928, 819 cm<sup>-1</sup>

Working Example 17 (Production of Compound 16)

- To a solution of 7-(4-methoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (170mg) in  
20 THF (10ml) were added at room temperature oxalyl chloride (0.09ml) and a drop of DMF, and the mixture was stirred for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (15ml). The solution was added dropwise at 0°C to a solution of 4-[N-(4,4-  
25 ethylenedioxcyclohexyl)-N-methylaminomethyl]aniline (0.15g) and triethylamine (0.14ml) in THF (5ml), and the mixture was stirred at room temperature for 21 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with  
30 saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:1) and recrystallized from ethanol/ethyl acetate) to give pale yellow crystals of  
35 N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-7-(4-methoxyphenyl)-1,1-

dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
(Compound 16) (164.2mg).

m.p. 222-228 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45-1.90 (8H, m), 2.20 (3H, s),  
5 2.45-2.63 (1H, m), 3.13-3.20 (2H, m), 3.56 (2H, s), 3.69-3.76  
(2H, m), 3.88 (3H, s), 3.95 (4H, s), 7.02 (2H, d, J=8.6 Hz),  
7.30-7.35 (3H, m), 7.52-7.70 (6H, m), 7.92 (1H, br s), 8.20  
(1H, d, J=8.0 Hz).

10 IR (KBr) 3356, 1651, 1608, 1518, 1311, 1292, 1252, 1126,  
824 cm<sup>-1</sup>

Anal. for C<sub>34</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 67.75 ; H, 6.35 ; N, 4.65

Found. C, 67.48 ; H, 6.15 ; N, 4.47.

Working Example 18 (Production of Compound 17)

15 To a solution of N-[4-[N-(4,4-  
ethylenedioxycyclohexyl)-N-methylaminomethyl]phenyl]-7-  
(4-methoxyphenyl)-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (112mg) in THF (20ml) was added  
at room temperature 3N hydrochloric acid (1ml), and the  
20 mixture was stirred for 18 hours. To the mixture was added  
saturated sodium bicarbonate solution, and the mixture was  
extracted with ethyl acetate. The organic layer was washed  
with saturated brine, dried with magnesium sulfate and  
concentrated under reduced pressure to give colorless solid,  
25 which was recrystallized from ethyl acetate/hexane to give  
colorless crystals of 7-(4-methoxyphenyl)-N-[4-[N-  
methyl-N-(4-oxocyclohexyl)aminomethyl]phenyl]-1,1-  
dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
(Compound 17) (77.6mg).

30 m.p. 214-218 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.77-2.14 (4H, m), 2.24 (3H, s),  
2.26-2.58 (4H, m), 2.80-2.96 (1H, m), 3.13-3.20 (2H, m),  
3.61 (2H, s), 3.70-3.76 (2H, m), 3.87 (3H, s), 7.02 (2H,  
d, J=8.8 Hz), 7.32-7.36 (3H, m), 7.53-7.70 (6H, m), 7.97  
35 (1H, br s), 8.20 (1H, d, J=8.4 Hz).

IR (KBr) 3280, 1713, 1657, 1603, 1518, 1313, 1296, 1252,

1128, 825  $\text{cm}^{-1}$

Anal. for  $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_5\text{S}\cdot 0.5\text{H}_2\text{O}$

Calcd. C, 67.70 ; H, 6.21 ; N, 4.93

Found. C, 67.58 ; H, 5.97 ; N, 4.66.

5 Working Example 19 (Production of Compound 18)

To a solution of 7-(4-ethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (10ml) were added at room temperature oxalyl chloride (0.09ml) and a drop of DMF, and the mixture was stirred for  
10 1 hour. The mixture was concentrated under reduced pressure, and the residue was dissolved in THF (10ml). The solution was added dropwise at  $0^\circ\text{C}$  to a solution of 4-[N-(4,4-ethylenedioxycyclohexyl)-N-methylaminomethyl]aniline [0.153g (0.553mmol)] and triethylamine (0.14ml) in THF (5ml),  
15 and the mixture was stirred at room temperature for 16 hours.

To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give crude  
20 crystals, which were recrystallized from ethanol/diisopropylether to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[N-(4,4-ethylenedioxycyclohexyl)-N-methylaminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
25 (Compound 18) (187mg).

m.p. 220-223  $^\circ\text{C}$

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.46 (3H, t,  $J=7.0$  Hz), 1.51-1.92 (8H, m), 2.21 (3H, s), 2.46-2.64 (1H, m), 3.17 (2H, t,  $J=7.0$  Hz), 3.57 (2H, s), 3.73 (2H, t,  $J=7.0$  Hz), 3.95 (4H, s), 4.10  
30 (2H, q,  $J=7.0$  Hz), 7.01 (2H, d,  $J=9.0$  Hz), 7.28-7.38 (3H, m), 7.49-7.59 (4H, m), 7.61-7.72 (2H, m), 7.87-7.94 (1H, m), 8.21 (1H, d,  $J=8.2$  Hz).

IR (KBr) 3346, 1651, 1518, 1311, 1292, 1250, 1164, 1126, 822  $\text{cm}^{-1}$

35 Anal. for  $\text{C}_{35}\text{H}_{40}\text{N}_2\text{O}_6\text{S}\cdot 0.2\text{H}_2\text{O}$

Calcd. C, 67.76 ; H, 6.56 ; N, 4.52

Found. C, 67.66 ; H, 6.32 ; N, 4.36.

Working Example 20 (Production of Compound 19)

To a solution of 7-(4-ethoxyphenyl)-N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (140mg) in THF (20ml) was added at room temperature 3N hydrochloric acid (1ml), and the mixture was stirred for 40 hours. To the mixture was added saturated sodium bicarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give colorless solid, which was recrystallized from ethyl acetate/hexane to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[N-methyl-N-(4-oxocyclohexyl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 19) (101.1mg).

m.p. 195 °C (dec.)

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45 (3H, t, J=7.0 Hz), 1.83-2.17 (4H, m), 2.24 (3H, s), 2.26-2.59 (4H, m), 2.80-2.98 (1H, m), 3.13-3.20 (2H, m), 3.62 (2H, s), 3.69-3.76 (2H, m), 4.10 (2H, q, J=7.0 Hz), 7.01 (2H, d, J=8.8 Hz), 7.32-7.36 (3H, m), 7.52-7.70 (6H, m), 7.96 (1H, br s), 8.20 (1H, d, J=8.4 Hz).

IR (KBr) 3278, 1713, 1657, 1603, 1520, 1313, 1298, 1248, 1128, 824 cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>·1.0H<sub>2</sub>O

Calcd. C, 67.10 ; H, 6.48 ; N, 4.74

Found. C, 66.97 ; H, 6.09 ; N, 4.72.

Working Example 21 (Production of Compound 20)

To a solution of 7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzoxepine-4-carboxylic acid (180mg) in THF (10ml) were added at room temperature oxalyl chloride (0.09ml) and a drop of DMF, and the mixture was stirred for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (15ml), and the solution was added

- dropwise at 0°C to a solution of 4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]aniline (0.153g) and triethylamine (0.14ml) in THF (5ml). The mixture was stirred at room temperature for 15 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate= 1:1) and recrystallized from ethanol/diisopropylether to give pale yellow crystals of N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 20) (153.1mg).
- m.p. 214-215 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45-1.92 (8H, m), 2.20 (3H, s), 2.43-2.62 (1H, m), 3.17 (2H, t, J=7.0 Hz), 3.57 (2H, s), 3.69-3.76 (2H, m), 3.95 (4H, s), 6.04 (2H, s), 6.92 (1H, d, J=8.6 Hz), 7.07-7.12 (2H, m), 7.31-7.35 (3H, m), 7.51-7.66 (4H, m), 7.88 (1H, br s), 8.19 (1H, d, J=8.4 Hz).
- IR (KBr) 3327, 1649, 1514, 1314, 1292, 1238, 1128, 1109, 930, 818 cm<sup>-1</sup>
- Anal. for C<sub>34</sub>H<sub>36</sub>N<sub>2</sub>O<sub>7</sub>S·0.1H<sub>2</sub>O
- Calcd. C, 66.02 ; H, 5.90 ; N, 4.53
- Found. C, 65.98 ; H, 5.78 ; N, 4.23.
- Working Example 22 (Production of Compound 21)
- To a solution of N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (100mg) in THF (10ml) was added at room temperature 3N hydrochloric acid (1ml), and the mixture was stirred for 39 hours. To the mixture was added saturated sodium bicarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and

concentrated under reduced pressure to give colorless solid which were recrystallized from ethyl acetate to give colorless crystals of 7-(3,4-methylenedioxyphenyl)-N-[4-[N-methyl-N-(4-oxocyclohexyl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 21) (56.8mg).

m.p. 219-223 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.83-2.17 (4H, m), 2.24 (3H, s), 2.29-2.59 (4H, m), 2.81-2.98 (1H, m), 3.16 (2H, t, J=6.9 Hz), 3.61 (2H, s), 3.73 (2H, t, J=6.9 Hz), 6.05 (2H, s), 6.92 (1H, d, J=8.4 Hz), 7.07-7.12 (2H, m), 7.32-7.36 (3H, m), 7.54-7.59 (3H, m), 7.64 (1H, dd, J=8.0, 2.0 Hz), 7.98 (1H, br s), 8.19 (1H, d, J=8.0 Hz).

IR (KBr) 3280, 1716, 1659, 1599, 1510, 1479, 1410, 1317, 1292, 1234, 1128, 1041, 812 cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>S·0.5H<sub>2</sub>O

Calcd. C, 66.08 ; H, 5.72 ; N, 4.82

Found. C, 66.36 ; H, 5.73 ; N, 4.78.

Working Example 23 (Production of Compound 22)

To a solution 7-(4-chlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (250mg) in THF (10ml) were added at room temperature oxalyl chloride (0.13ml) and a drop of DMF, and the mixture was stirred for 1 hour and concentrated under reduced pressure. The residue was dissolved in THF (15ml), and the solution was added dropwise at 0°C to a solution of 4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]aniline (0.238g) and triethylamine (0.2ml) in THF (5ml). The mixture was stirred at room temperature for 20 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate= 1:2) and recrystallized from ethanol to give colorless crystals of 7-(4-



chlorophenyl)-N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 22) (286.8mg).  
m.p. 224-228 °C

- 5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.44-1.90 (8H, m), 2.20 (3H, s), 2.42-2.64 (1H, m), 3.12-3.23 (2H, m), 3.56 (2H, s), 3.70-3.77 (2H, m), 3.95 (4H, s), 7.31-7.35 (3H, m), 7.45-7.57 (6H, m), 7.63-7.73 (2H, m), 7.90 (1H, br s), 8.24 (1H, d, J=8.4 Hz).
- 10 IR (KBr) 3336, 1672, 1518, 1308, 1282, 1165, 1126, 1097, 820 cm<sup>-1</sup>  
Anal. for C<sub>33</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub>SCl  
Calcd. C, 65.28 ; H, 5.81 ; N, 4.61  
Found. C, 65.18 ; H, 5.70 ; N, 4.60.
- 15 Working Example 24 (Production of Compound 23)  
To a solution of 7-(4-chlorophenyl)-N-[4-[N-(4,4-ethylenedioxcyclohexyl)-N-methylaminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (180mg) in THF (15ml) was added at room temperature 3N  
20 hydrochloric acid (1ml), and the mixture was stirred for 7 days. To the mixture was added saturated sodium bicarbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under  
25 reduced pressure to give colorless solid, which was recrystallized from ethyl acetate to give colorless crystals of 7-(4-chlorophenyl)-N-[4-[N-methyl-N-(4-oxocyclohexyl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 23)  
30 (85.9mg).  
m.p. 197-200 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.79-2.20 (4H, m), 2.25 (3H, s), 2.29-2.62 (4H, m), 2.84-3.03 (1H, m), 3.18 (2H, t, J=7.0 Hz), 3.63 (2H, s), 3.70-3.78 (2H, m), 7.30-7.72 (11H, m),  
35 7.84-8.02 (1H, m), 8.24 (1H, d, J=8.4 Hz).  
IR (KBr) 3277, 1714, 1653, 1599, 1529, 1410, 1319, 1128,

820  $\text{cm}^{-1}$

Anal. for  $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_4\text{SCl}\cdot 0.75\text{H}_2\text{O}$

Calcd. C, 64.57 ; H, 5.68 ; N, 4.86

Found. C, 64.49 ; H, 5.40 ; N, 4.92.

5 Working Example 25 (Production of Compound 24)

To a solution of 7-(4-morpholinophenyl)-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxylic acid (150mg) and  
1-hydroxybenzotriazole (101mg) in DMF (5ml) was added at  
room temperature 1-ethyl-3-(3'-  
10 dimethylaminopropyl)carbodiimide hydrochloride (144mg),  
and the mixture was stirred for 2 hours. To the mixture were  
added a solution of ethyl 3-[N-(4-aminobenzyl)-N-  
methylamino]propionate (133mg) and triethylamine (0.1ml)  
in DMF (5ml) and a piece of 4-dimethylaminopyridine, and  
15 the mixture was stirred for 20 hours and concentrated under  
reduced pressure. To the residue was added water, and the  
mixture was extracted with dichloromethane. The organic  
layer was washed with saturated brine and dried with  
magnesium sulfate. The solvent was evaporated under  
20 reduced pressure, and the residue was purified with column  
chromatography (ethanol/ethyl acetate=1:9) and  
recrystallized from ethyl acetate/hexane to give yellow  
crystals of N-[4-[N-(2-ethoxycarbonylethyl)-N-  
methylaminomethyl]phenyl]-7-(4-morpholinophenyl)-1,1-  
25 dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
(Compound 24) (133.6mg).

m.p. 209-211  $^{\circ}\text{C}$

$^1\text{H}$ -NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.26 (3H, t,  $J=7.2$  Hz), 2.21 (3H, s),  
2.49-2.55 (2H, m), 2.72-2.79 (2H, m), 3.10-3.20 (2H, m),  
30 3.23-3.28 (4H, m), 3.51 (2H, s), 3.69-3.76 (2H, m), 3.87-3.92  
(4H, m), 4.15 (2H, q,  $J=7.2$  Hz), 7.00 (2H, d,  $J=9.2$  Hz),  
7.25-7.37 (3H, m), 7.53-7.58 (4H, m), 7.63-7.72 (2H, m),  
7.96 (1H, s), 8.19 (1H, d,  $J=8.0$  Hz).

IR (KBr) 3334, 1732, 1651, 1605, 1520, 1311, 1238, 1165,  
35 1126, 930, 818  $\text{cm}^{-1}$

Anal. for  $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_6\text{S}$

Calcd. C, 66.10 ; H, 6.36 ; N, 6.80

Found. C, 65.84 ; H, 6.44 ; N, 6.81.

Working Example 26 (Production of Compound 25)

- To a solution of 7-(4-trifluoromethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (5ml) were added at room temperature oxalyl chloride (0.08ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in DMF (4ml).
- The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (109mg) and triethylamine (0.19ml) in THF (5ml), and the mixture was stirred at room temperature for 18 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethanol to give colorless crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-trifluoromethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 25) (137.0mg).
- m.p. 261-263 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.52-1.82 (4H, m), 2.21 (3H, s), 2.52-2.74 (1H, m), 3.15-3.22 (2H, m), 3.31-3.45 (2H, m), 3.58 (2H, s), 3.71-3.78 (2H, m), 3.98-4.12 (2H, m), 7.27-7.35 (5H, m), 7.55 (2H, d, J=8.8 Hz), 7.61-7.65 (3H, m), 7.70 (1H, dd, J=8.1, 1.8 Hz), 7.93 (1H, br s), 8.25 (1H, d, J=8.1 Hz).
- IR (KBr) 3242, 1657, 1633, 1601, 1518, 1412, 1317, 1294, 1265, 1215, 1169, 1130 cm<sup>-1</sup>
- Anal. for C<sub>31</sub>H<sub>31</sub>N<sub>2</sub>O<sub>5</sub>SF<sub>3</sub>
- Calcd. C, 61.99 ; H, 5.20 ; N, 4.66
- Found. C, 61.95 ; H, 5.01 ; N, 4.59.
- Working Example 27 (Production of Compound 26)

To a solution of 7-(3,4-dichlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (10ml) were added at room temperature thionyl chloride (0.08ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (15ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (114mg) and triethylamine (0.2ml) in THF (2ml), and the mixture was stirred at room temperature for 16 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give colorless crystals of 7-(3,4-dichlorophenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 26) (155.0mg).

m.p. 235-237 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.56-1.78 (4H, m), 2.21 (3H, s), 2.55-2.73 (1H, m), 3.17 (2H, t, J=6.6 Hz), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.73 (2H, t, J=6.6 Hz), 3.98-4.10 (2H, m), 7.30-7.35 (3H, m), 7.43 (1H, dd, J=8.4, 2.2 Hz), 7.52-7.69 (6H, m), 7.96 (1H, br s), 8.25 (1H, d, J=8.2 Hz). IR (KBr) 3253, 1655, 1633, 1601, 1529, 1467, 1410, 1317, 1296, 1130, 818 cm<sup>-1</sup>

Anal. for C<sub>30</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>SCl<sub>2</sub>

Calcd. C, 61.54 ; H, 5.16 ; N, 4.78

Found. C, 61.71 ; H, 5.14 ; N, 4.77.

Working Example 28 (Production of Compound 27)

To a solution of 7-(4-propylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg) in THF (5ml) were added at room temperature thionyl chloride (0.09ml) and a drop of DMF, and the mixture was stirred for

- 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (12ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline [122mg (0.55mmol)] and triethylamine (0.14ml) in THF (2ml), and the mixture was stirred at room temperature for 4 hours.
- To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give pale yellow crystals, which were recrystallized from ethanol to give colorless crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 27) (195.0mg).
- m.p. 247-250 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.98 (3H, t, J=7.3 Hz), 1.56-1.83 (6H, m), 2.21 (3H, s), 2.52-2.74 (3H, m), 3.18 (2H, t, J=6.6 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.70-3.76 (2H, m), 3.97-4.10 (2H, m), 7.28-7.35 (5H, m), 7.52 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.66-7.73 (2H, m), 7.94 (1H, br s), 8.21 (1H, d, J=8.0 Hz).
- IR (KBr) 3250, 1657, 1635, 1599, 1525, 1410, 1315, 1296, 1165, 1130 cm<sup>-1</sup>.
- Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>S  
Calcd. C, 70.94 ; H, 6.86 ; N, 5.01  
Found. C, 70.99 ; H, 6.51 ; N, 5.05.
- Working Example 29 (Production of Compound 28)
- To a solution of 7-(4-isopropoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (400mg) in THF (10ml) were added at room temperature thionyl chloride (0.094ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (10ml). The solution was added dropwise at 0°C to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline

- (260mg) and triethylamine (0.45ml) in THF (2ml), and the mixture was stirred at room temperature for 18 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with
- 5 saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give pale yellow crystals, which were recrystallized from ethanol to give pale yellow crystals of 7-(4-isopropoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-
- 10 dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 28) (367.1mg).
- m.p. 245-247 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.38 (6H, d, J=5.8 Hz), 1.59-1.84 (4H, m), 2.21 (3H, s), 2.54-2.76 (1H, m), 3.16 (2H, t, J=7.0 Hz),
- 15 3.31-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 3.99-4.10 (2H, m), 4.56-4.69 (1H, m), 6.99 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.53 (2H, d, J=8.8 Hz), 7.55 (2H, d, J=8.8 Hz), 7.62-7.69 (2H, m), 7.93 (1H, br s), 8.19 (1H, d, J=8.4 Hz).
- IR (KBr) 3248, 1655, 1603, 1515, 1410, 1317, 1292, 1248,
- 20 1171, 1128, 825 cm<sup>-1</sup>
- Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>S
- Calcd. C, 68.96 ; H, 6.66 ; N, 4.87
- Found. C, 68.70 ; H, 6.34 ; N, 4.86.
- Working Example 30 (Production of Compound 29)
- 25 To a suspension of 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (170mg) in THF (5ml) were added at room temperature thionyl chloride (0.07ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure,
- 30 and the residue was dissolved in THF (10ml). The solution was added dropwise at room temperature to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (111mg) and triethylamine (0.18ml) in THF (2ml), and the mixture was stirred at room temperature for 21 hours. To
- 35 the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with

saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3) and recrystallized from ethanol to give pale yellow crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 29) (147.6mg).

m.p. 244-247 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J=7.4 Hz), 1.57-1.90 (6H, m), 2.21 (3H, s), 2.54-2.75 (1H, m), 3.13-3.20 (2H, m), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 3.98 (2H, t, J=6.6 Hz), 3.99-4.11 (2H, m), 7.01 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.52-7.56 (4H, m), 7.62 (1H, d, J=1.8 Hz), 7.67 (1H, dd, J=8.0, 1.8 Hz), 7.92 (1H, br s), 8.19 (1H, d, J=8.0 Hz).

IR (KBr) 3280, 1657, 1603, 1520, 1315, 1294, 1250, 1130, 822 cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 68.96 ; H, 6.66 ; N, 4.87

Found. C, 68.72 ; H, 6.70 ; N, 4.88.

Working Example 31 (Production of Compound 30)

To a solution of 7-(4-butoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg) in THF (5ml) were added at room temperature thionyl chloride (0.07ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (10ml). The solution was added dropwise at room temperature to a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (114mg) and triethylamine (0.2ml) in THF (2ml), and the mixture was stirred at room temperature for 3 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column

- chromatography (ethanol/ethyl acetate=1:4) and recrystallized from ethanol to give pale yellow crystals of 7-(4-butoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 30) (138.6mg).
- m.p. 233-236 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.00 (3H, t, J=7.3 Hz), 1.40-1.87 (8H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.16 (2H, t, J=6.8 Hz), 3.31-3.42 (2H, m), 3.58 (2H, s), 3.72 (2H, t, J=6.8 Hz), 3.98-4.10 (2H, m), 4.02 (2H, t, J=6.4 Hz), 7.00 (2H, d, J=8.8 Hz), 7.30-7.35 (3H, m), 7.54 (2H, d, J=8.8 Hz), 7.55 (2H, d, J=8.8 Hz), 7.62-7.69 (2H, m), 7.93 (1H, br s), 8.19 (1H, d, J=8.0 Hz)
- IR (KBr) 3280, 1659, 1603, 1518, 1315, 1294, 1250, 1128, 825 cm<sup>-1</sup>
- Anal. for C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S
- Calcd. C, 69.36 ; H, 6.85 ; N, 4.76
- Found. C, 69.20 ; H, 6.75 ; N, 4.94.

Working Example 32 (Production of Compound 31)

- To a suspension of 6-(4-methylphenyl)-1,1-dioxo-1,2-dihydro-2H-thiochromene-3-carboxylic acid (178 mg, 0.567 mmol) and HOBt (115 mg, 0.85 mmol) in acetonitrile (5 ml) was added WSC (163 mg, 0.85 mmol), and the mixture was stirred for 1 hour. To the mixture was added a solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (187 mg, 0.85 mmol) and triethylamine (0.16 ml, 1.13 mmol) in acetonitrile (1 ml), and the mixture was stirred for 15 hours. The solvent was evaporated, and the residue was diluted with ethyl acetate. The mixture was washed with water and saturated brine, and dried with magnesium sulfate. The solvent was evaporated, and the residue was subjected to silica gel column chromatography to give, from the fraction eluted with ethyl acetate/ethanol (2:1), 6-(4-methylphenyl)-N-(4-((N-methyl-N-tetrahydropyran-4-ylamino)methyl)phenyl)-1,1-dioxo-1,2-dihydro-2H-



thiochromene-3-carboxamide (Compound 31) (89.4 mg, 31%) as brown powder.

m.p. 197°C (decomp.).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.96-8.02 (3H, m), 7.86 (1H, s),

5 7.65-7.71 (4H, m), 7.25-7.38 (4H, m), 4.57 (2H, s), 3.81-4.00 (2H, m), 3.54 (2H, s), 3.20-3.32 (2H, m), 2.50-2.72 (1H, m), 2.39 (3H, s), 2.12 (3H, s).

Working Example 33 (Production of Compound 32)

To a suspension of 7-(4-methylphenyl)-1,1-dioxo-  
10 2,3-dihydro-1-benzothiepine-4-carboxylic acid (325 mg, 0.991 mmol) in THF (10 ml) were added at 0°C oxalyl chloride (0.26 ml, 2.97 mmol) and DMF (1 drop), and the mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated, and the residue was dissolved in THF (8 ml).

15 To the solution was added dropwise a solution of 4-(N-(3-ethoxycarbonylethyl)-N-methyl)aminomethyl)aniline (257 mg, 1.09 mmol) and triethylamine (0.42 ml, 2.97 mmol) in THF (2 ml) at 0°C, and the mixture was stirred at room temperature for 17 hours. To the mixture was added water,

20 and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was subjected to silica gel column chromatography to give, from the fraction eluted with ethyl acetate,

25 N-(4-(N-(3-ethoxycarbonylethyl)-N-methyl)aminomethyl)phenyl-7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 32) (310 mg, 57%), which was recrystallized from acetone/ethanol to give colorless crystals having m.p. 180°C.

30 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.20 (1H, d, J=8.0), 7.98 (1H, br s), 7.64-7.71 (2H, m), 7.47-7.57 (4H, m), 7.26-7.36 (4H, m), 4.15 (2H, q, J=7.4), 3.72 (2H, t, J=6.7), 3.51 (2H, s), 3.16 (2H, t, J=6.7), 2.76 (2H, t, J=7.0), 2.52 (2H, t, J=7.0), 2.42 (3H, s), 2.21 (3H, s), 1.26 (3H, t, J=7.4).

35 Working Example 34 (Production of Compound 33)

To a suspension of 6-(4-methylphenyl)-1,1-dioxo-

1,2-dihydro-2H-thiochromene-3-carboxylic acid (115 mg, 0.494 mmol) in THF (5 ml) were added oxalyl chloride (0.13 ml, 1.48 mmol) and DMF (1 drop), and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (5 ml). To the solution was added a solution of 4-(N-(2-methoxyethyl)-N-methyl)aminomethylaniline (127 mg, 0.543 mmol) and triethylamine (0.21 ml, 1.48 mmol) in THF (2 ml), and the mixture was stirred for 15 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated, and the residue was subjected to silica gel column chromatography to give, from the fraction eluted with ethyl acetate/ethanol (4:1), N-(4-(N-(4-methoxyethyl)-N-methyl)aminomethyl)phenyl-6-(4-methylphenyl)-1,1-dioxo-1,2-dihydro-2H-thiochromene-3-carboxamide (Compound 33) (110 mg, 42%) as dark green crystals. m.p. 138°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.19 (1H, br s), 7.90 (2H, d, J=8.4), 7.56 (2H, dd, J=8.0, 8.1), 7.32-7.48 (5H, m), 7.17-7.22 (4H, m), 4.21 (2H, s), 3.44 (2H, s), 3.43 (2H, t, J=5.6), 3.25 (3H, s), 2.51 (2H, t, J=5.6), 2.32 (3H, s), 2.17 (3H, s).  
Anal. Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>S · 0.5H<sub>2</sub>O: C; 67.31, H; 6.25, N; 5.61.  
Found: C; 67.61, H; 5.98, N; 5.33.

Working Example 35 (Production of Compound 34)

To a solution of 7-(4-methylphenyl)-N-(4-(N-methyl-N-tetrahydropyran-4-ylamino)methyl)phenyl-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (137 mg, 0.258 mmol) in DMF (2 ml) was added methyl iodide (0.02 ml, 0.284 mmol), and the mixture was stirred for 16 hours. The solvent was evaporated to give powder, which was washed with hexane to give dimethyl (N-(7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carbonyl-4-aminobenzyl)-N-(tetrahydropyran-4-yl)ammonium chloride (Compound 34) (164 mg, 95%) as brown powder.

m.p. 170-171°C.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 9.46 (1H, s), 8.04-8.11 (2H, m), 7.84-7.86 (3H, m), 7.72 (2H, d, J=8.4), 7.52-7.61 (2H, m), 7.36 (2H, d, J=7.4), 4.47 (2H, s), 4.00-4.14 (2H, m), 3.83 (2H, t, J=6.2), 3.50-3.71 (1H, m), 2.88 (6H, s), 2.38 (3H, s), 2.10-2.22 (2H, m), 1.79-2.00 (2H, m).

Anal. Calcd for C<sub>32</sub>H<sub>37</sub>IN<sub>2</sub>O<sub>4</sub>S · H<sub>2</sub>O: C; 55.65, H; 5.69, N; 4.06. Found: C; 55.65, H; 5.64, N; 4.17.

Working Example 36 (Production of Compound 35)

10 To a solution of 7-(4-methylphenyl)-N-(4-((N-methyl-N-(3-pentyl)amino)methyl)phenyl-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (119 mg, 0.321 mmol) in DMF (2 ml) was added methyl iodide (0.025 ml, 0.353 mmol), and the mixture was stirred for 16 hours. The solvent was  
15 evaporated to give powder, which was washed with hexane to give dimethyl (N-(1,1-dioxo-7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxyl-4-aminobenzyl)-N-(3-pentyl)ammonium chloride (Compound 35) (114 mg, 95%).  
m.p. 150-151°C.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 9.48 (1H, br s), 8.22 (1H, br s), 8.13 (2H, d, J=8.0), 7.86-7.92 (2H, m), 7.45-7.76 (4H, m), 7.24-7.29 (2H, m), 4.74 (2H, s), 3.76 (2H, t, J=5.2), 3.20-3.37 (1H, m), 3.02 (2H, t, J=5.2), 2.98 (6H, s), 2.38 (3H, s), 1.50-1.80 (4H, m), 1.08 (6H, t, J=7.4).

25 Anal. Calcd for C<sub>32</sub>H<sub>39</sub>IN<sub>2</sub>O<sub>3</sub>S · 1.5H<sub>2</sub>O: C; 56.06, H; 6.17, N; 4.09. Found: C; 55.47, H; 5.90, N; 4.38.

Working Example 37 (Production of Compound 36)

To a solution of 7-(4-methylphenyl)-N-(4-((N-methyl-N-tetrahydropyran-4-yl)aminomethyl)phenyl)-2,3-dihydro-1-benzothiepine-4-carboxamide (0.2g) in  
30 dichloromethane (50ml) was added at -30 to -10°C 70% mCPBA (0.1g), and the mixture was stirred at -30 to -10°C for 1 hour. To the mixture was added an aqueous solution of sodium thiosulfate, and the mixture was concentrated and extracted  
35 with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated

brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (methanol/dichloromethane) to give crude crystals, which  
5 were recrystallized from ethyl acetate/hexane to give 7-(4-methylphenyl)-N-(4-((N-methyl-N-tetrahydropyran-4-yl)aminomethyl)phenyl)-1-oxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 36) (0.04g) as colorless crystals.  
10 mp 191-192°C.  
<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.65-1.80 (4H, m), 2.22 (3H, s), 2.41 (3H, s), 2.55-2.90 (2H, m), 3.10-3.25 (1H, m), 3.35-3.50 (3H, m), 3.58 (2H, s), 3.81-3.95 (1H, m), 4.01-4.11 (2H, m), 7.25 (2H, d, J=8.0Hz), 7.33 (2H, d, J=8.5Hz), 7.45 (2H, d, J=8.0Hz), 7.52 (1H, s), 7.61 (2H, d, J=8.5Hz), 7.70 (1H, dd, J=2.0, 8.2Hz), 7.97 (1H, d, J=8.0Hz), 8.26 (1H, s).  
15 IR(KBr) ν: 2948, 2845, 1663cm<sup>-1</sup>.

Working Example 38 (Production of Compound 37)

In dichloromethane (10ml) was suspended 7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.3g), and to the suspension were added under ice-cooling oxalyl chloride (0.25ml) and dimethylformamide (catalytic amount). The mixture was stirred at room temperature for 2 hours, and the solvent  
20 was evaporated. The residue was dissolved in tetrahydrofuran (20ml), and the solution was added dropwise to a solution of 4-(N-methyl-N-(tetrahydropyran-4-yl)aminomethyl)aniline (0.22g) and triethylamine (0.38ml) in tetrahydrofuran (25ml) under ice-cooling. Under  
25 nitrogen atmosphere, the mixture was stirred overnight at room temperature, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate.  
30 Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl

acetate/hexane to give 7-(4-methylphenyl)-N-(4-((N-methyl-N-tetrahydropyran-4-yl)aminomethyl)phenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 39) (0.22g) as pale yellow crystals.

5 mp 234-235°C(dec.).

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.67-1.75 (4H, m), 2.21 (3H, s), 2.42 (3H, s), 2.57-2.70 (1H, m), 3.17 (2H, t, J=6.8Hz), 3.37 (2H, dt, J=2.6, 11.2Hz), 3.58 (2H, s), 3.73 (2H, t, J=6.8Hz), 4.01-4.11 (2H, m), 7.27-7.36 (4H, m), 7.49-7.57 (4H, m), 7.65 (1H, s), 7.70 (1H, dd, J=2.0, 8.2Hz), 7.94 (1H, s), 8.21 (1H, d, J=8.2Hz).

10 IR(KBr) ν: 2946, 2845, 1667cm<sup>-1</sup>.

Anal. Calcd. for C<sub>31</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>S: C, 70.16; H, 6.46; N, 5.28.

Found C, 69.95; H, 6.22; N, 5.16.

15 Working Example 39 (Production of Compound 38)

To a suspension of 7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.25g) in dichloromethane (8ml) were added, under ice-cooling, oxalyl chloride (0.2ml) and dimethylformamide (catalytic amount),

20 and the mixture was stirred at room temperature for 2 hours.

The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (15ml). The solution was added dropwise to a solution of 4-((N-methyl-N-(pentan-3-

25 yl))aminomethyl)aniline (0.17g) and triethylamine (0.32ml) in tetrahydrofuran (15ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred overnight at room temperature, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and

30 saturated brine, and dried with anhydrous magnesium sulfate.

Under reduced pressure, the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-methyl-N-(pentan-3-yl))aminomethyl)phenyl)-7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 38)

35 (0.13g) as colorless crystals.

mp 130-131°C.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 0.94 (6H, t, J=7.3Hz), 1.27-1.58 (4H, m), 2.15 (3H, s), 2.28-2.38 (1H, m), 2.42 (3H, s), 3.17 (2H, t, J=6.8Hz), 3.58 (2H, s), 3.72 (2H, t, J=6.8Hz), 7.27-7.37 (4H, m), 7.49-7.56 (4H, m), 7.66-7.72 (2H, m), 7.97 (1H, s), 8.21 (1H, d, J=8.0Hz).

IR(KBr) ν: 2963, 2930, 1663cm<sup>-1</sup>.

Anal. Calcd. for C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>3</sub>S·0.5H<sub>2</sub>O: C, 70.83; H, 7.09; N, 5.33. Found C, 70.77; H, 6.76; N, 5.45.

10 Working Example 40 (Production of Compound 39)

In dichloromethane (5ml) was suspended 7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.3g). To the suspension were added, under ice-cooling, oxalyl chloride (0.25ml) and dimethylformamide (catalytic amount), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated, and the residue was dissolved in tetrahydrofuran (20ml). The solution was added dropwise to a solution of N-(4-aminobenzyl)sarcosine methyl ester (0.21g) and triethylamine (0.38ml) in tetrahydrofuran (10ml), under ice-cooling. Under nitrogen atmosphere, the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give crude crystals, which were recrystallized from ethyl acetate/hexane to give N-(4-((N-methoxycarbonylmethyl-N-methyl)aminomethyl)phenyl)-7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 39) (0.22g) as colorless crystals.

mp 136-143°C.

35 <sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 2.39 (3H, s), 2.43 (3H, s), 3.17 (2H, t, J=6.6Hz), 3.27 (2H, s), 3.66 (2H, s), 3.69-3.76 (2H, m),

3.72 (3H, s), 7.28-7.37 (4H, m), 7.48-7.58 (4H, m), 7.65 (1H, s), 7.70 (1H, dd, J=1.6, 8.4Hz), 7.93 (1H, s), 8.21 (1H, d, J=8.4Hz).

IR(KBr)  $\nu$ : 2932, 1744cm<sup>-1</sup>.

5 Anal. Calcd. for C<sub>29</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>S: C, 67.16; H, 5.83; N, 5.40.

Found C, 66.94; H, 5.94; N, 5.20.

Working Example 41 (Production of Compound 40)

In THF (6.5ml) was dissolved 7-(5-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (166mg), and to the solution were added, under ice-cooling and stirring, oxalyl chloride (0.087ml) and DMF (one drop). The mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (6ml). The solution was added dropwise, under ice-cooling, to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (135mg) and triethylamine (0.2ml) in THF (4ml), and the mixture was stirred at room temperature for 13 hours. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=3/1) and recrystallized from ethanol to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(5-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 40) (113mg).  
m.p. 229-231°C

30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>)  $\delta$  1.60-1.82 (4H, m), 2.21 (3H, s), 2.54 (3H, s), 2.65 (1H, m), 3.37 (2H, td, J=11.4, 3.0Hz), 3.57 (2H, s), 3.70 (2H, m), 4.01-4.07 (2H, m), 6.79 (1H, dd, J=3.6, 1.0Hz), 7.24-7.34 (3H, m), 7.53-7.64 (4H, m), 8.01 (1H, s), 8.11 (1H, d, J=8.4Hz)

35 IR (KBr) 1659, 1526, 1410, 1318, 1292, 1128, 806cm<sup>-1</sup>

Working Example 42 (Production of Compound 41)

In THF (16ml) was dissolved 7-(4-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (400mg), and to the stirred solution were added under ice-cooling oxalyl chloride (0.21ml) and DMF (one drop). The mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (6ml). The solution was added dropwise to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (352mg) and triethylamine (0.5ml) in THF (10ml), under ice-cooling, and the mixture was stirred at room temperature for 15 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=3/1) and recrystallized from ethanol to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 41) (355mg).

m.p. 232-234°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.57-1.83 (4H, m), 2.21 (3H, s), 2.54 (3H, s), 2.65 (1H, m), 3.13 (2H, t, J=6.6Hz), 3.38 (2H, td, J=11.4, 2.8Hz), 3.57 (2H, s), 3.70 (2H, t, J=6.6Hz), 4.00-4.08 (2H, m), 7.00 (1H, s), 7.23-7.34 (3H, m), 7.53-7.64 (4H, m), 8.10 (2H, d, J=8.0Hz)

IR (KBr) 1643, 1518, 1408, 1319, 1294, 817cm<sup>-1</sup>

Working Example 43 (Production of Compound 42)

In THF (8.0ml) was dissolved 7-(5-chloro-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg), and to the stirred solution were added under ice-cooling oxalyl chloride (0.075ml) and DMF (one drop). The mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (8ml). The solution



- was added dropwise to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (153mg) and triethylamine (0.20ml) in THF (6ml), under ice-cooling, and the mixture was stirred at room temperature
- 5 for 16 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography
- 10 (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give 7-(5-chloro-2-thienyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 42) (90mg).
- 15 m.p. 221-222°C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.60-1.83 (4H, m), 2.22 (3H, s), 2.67 (1H, m), 3.14 (2H, m), 3.37 (2H, td, J=11.4, 2.6Hz), 3.59 (2H, s), 3.71 (2H, m), 4.00-4.08 (2H, m), 6.97 (1H, d, J=4.0Hz), 7.22 (1H, J=4.0Hz), 7.33 (3H, d, J=8.8Hz),
- 20 7.51-7.61 (4H, m), 8.00 (1H, s), 8.14 (1H, d, J=8.0Hz)
- IR (KBr) 1655, 1528, 1410, 1318, 1294, 1130, 819cm<sup>-1</sup>
- Anal. for C<sub>28</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub>
- Calcd. C, 60.36 ; H, 5.25 ; N, 5.03
- Found. C, 60.56 ; H, 5.37 ; N, 4.93
- 25 Working Example 44 (Production of Compound 43)
- In THF (8ml) was dissolved 7-[(4-methylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (133mg), and to the stirred solution were added at room temperature oxalyl chloride
- 30 (0.065ml) and DMF (one drop). The mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (6ml). The solution was added dropwise to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-
- 35 yl)aminomethyl]aniline (100mg) and triethylamine (0.15ml) in THF (6ml), under ice-cooling, and the mixture was stirred

at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[(4-methylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 43) (80mg).  
m.p. 249-252°C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ (3H, t, J=7.2Hz), 1.58-2.00 (4H, m), 2.32 (3H, s), 2.54 (3H, s), 2.87 (1H, m), 3.16 (2H, t, J=6.6Hz), 3.30 (2H, td, J=11.4, 2.6Hz), 3.74 (4H, m), 3.94-4.10 (2H, m), 7.27-7.81 (12H, m), 8.20 (1H, d, J=8.4Hz)  
IR (KBr) 1653, 1530, 1410, 1318, 1294, 1130, 812cm<sup>-1</sup>  
Working Example 45 (Production of Compound 44)

In THF (4ml) was dissolved 7-[(4-ethylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (130mg), and to the stirred solution were added at room temperature thionyl chloride (0.035ml) and DMF (0.02ml). The mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (6ml).  
The solution was added dropwise to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (130mg) and triethylamine (0.3ml) in THF (6ml), under ice-cooling, and the mixture was stirred at room temperature for 4 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give 7-[(4-ethylthio)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-

2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 44)  
(82mg).

m.p. 232-233°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.37 (3H, t, J=7.2Hz), 1.58-1.82 (4H, m), 2.21 (3H, s), 2.66 (1H, m), 3.02 (2H, q, J=7.2Hz), 3.16 (2H, m), 3.37 (2H, td, J=11.4, 2.6Hz), 3.58 (2H, s), 3.72 (2H, m), 4.00-4.08 (2H, m), 7.30-7.70 (11H, m), 8.01 (1H, s), 8.20 (1H, d, J=8.0Hz)

IR (KBr) 1655, 1522, 1410, 1315, 1294, 1130, 816cm<sup>-1</sup>

10 Working Example 46 (Production of Compound 45)

In THF (10ml) was dissolved 7-[(4-ethylsulfonyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (250mg), to the stirred solution were added at room temperature thionyl chloride (0.054ml) and DMF (one drop). The mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (8ml). The solution was added dropwise to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline (167mg) and triethylamine (0.43ml) in THF (8ml), under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give 7-[(4-ethylsulfonyl)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 45) (105mg).

m.p. 210-211°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.32 (3H, t, J=7.2Hz), 1.56-1.83 (4H, m), 2.21 (3H, s), 2.65 (1H, m), 3.16 (2H, q, J=7.2Hz), 3.19 (2H, m), 3.37 (2H, td, J=11.4, 3.0Hz), 3.58 (2H, s), 3.74

(2H, m), 4.01-4.07 (2H, m), 7.33 (2H, d, J=8.4Hz), 7.38 (1H, s), 7.55 (2H, d, J=8.4Hz), 7.69-7.80 (4H, s), 7.99-8.05 (3H, m), 8.29 (2H, d, J=8.0Hz)

IR (KBr) 1659, 1530, 1410, 1313, 1294, 1146, 747, 733cm<sup>-1</sup>

5 Working Example 47 (Production of Compound 46)

In THF (10ml) was dissolved 1,1-dioxo-7-[(4-propylthio)phenyl]-2,3-dihydro-1-benzothiepine-4-carboxylic acid (400mg), and to the stirred solution were added at room temperature thionyl chloride (0.089ml) and  
10 DMF (one drop). The mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (8ml). The solution was added dropwise to a stirred solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]aniline  
15 (280mg) and triethylamine (0.57ml) in THF (8.4ml), under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under  
20 reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-7-[(4-propylthio)phenyl]-2,3-dihydro-1-benzothiepine-4-  
25 carboxamide (Compound 46) (298mg).  
m.p. 220-220°C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J=7.2Hz), 1.60-1.81 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 2.97 (2H, t, J=7.4Hz), 3.17  
30 (2H, m), 3.37 (2H, td, J=11.2, 2.8Hz), 3.58 (2H, s), 3.72 (2H, m), 4.00-4.09 (2H, m), 7.29-7.70 (11H, m), 7.95 (1H, s), 8.21 (1H, d, J=8.0Hz)  
Anal. for C<sub>33</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>  
Calcd. C, 67.09 ; H, 6.48 ; N, 4.74  
35 Found. C, 67.15 ; H, 6.27 ; N, 4.98  
IR (KBr) 1660, 1516, 1410, 1314, 1294, 1130, 816cm<sup>-1</sup>

## Working Example 48 (Production of Compound 47)

In THF (10ml) was dissolved 7-[(4-butylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (400mg), and to the stirred  
5 solution were added at room temperature thionyl chloride (0.086ml) and DMF (one drop). The mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (8ml). The solution was added dropwise to a stirred  
10 solution of 4-[N-methyl-N-(tetrahydropyran-4-yl)]aniline (270mg) and triethylamine (0.55ml) in THF (8.1ml), under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with  
15 saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give 7-[(4-butylthio)phenyl]-N-[4-[N-methyl-  
20 N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 47) (267mg).

m.p. 207-209°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.0Hz), 1.42-1.75 (8H,  
25 m), 2.21 (3H, s), 2.65 (1H, m), 2.99 (2H, t, J=7.2Hz), 3.16 (2H, m), 3.37 (2H, td, J=11.2, 3.0Hz), 3.57 (2H, s), 3.72 (2H, m), 4.01-4.09 (2H, m), 7.30-7.70 (11H, m), 7.96 (1H, s), 8.21 (1H, d, J=8.2Hz)

IR (KBr) 1653, 1530, 1410, 1318, 1294, 1130, 816cm<sup>-1</sup>

30 Anal. for C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>

Calcd. C, 67.52 ; H, 6.67 ; N, 4.63

Found. C, 67.66 ; H, 6.52 ; N, 4.87

## Reference Example 1

To a suspension of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (3.00g) in acetic acid (30ml)  
35 was added at room temperature 30% hydrogen peroxide solution

(4.5ml), and the mixture was refluxed for 1 hour. The reaction mixture was added to a stirred water, and precipitated crystals were collected by filtration. The crystals were washed with water and diisopropylether to give  
5 colorless crystals of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (3.06g).  
m.p. 162-164 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.11 (2H, t, J=6.5 Hz), 3.62 (2H, t, J=6.5 Hz), 3.87 (3H, s), 7.64-7.76 (3H, m), 8.03 (1H, d, J=8.4 Hz).  
10 IR (KBr) 1718, 1288, 1263, 1165, 1128, 1090, 797, 748 cm<sup>-1</sup>  
Anal. for C<sub>12</sub>H<sub>11</sub>O<sub>4</sub>SBr  
Calcd. C, 43.52 ; H, 3.35  
Found. C, 43.52 ; H, 3.18.

15 Reference Example 2

To a solution of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.8g) in THF (10ml) was added at 0°C 70% 3-chloroperbenzoic acid (1.45g), and the mixture was stirred at 0°C for 30 minutes and further at room  
20 temperature for 1 hour. To the mixture was added an aqueous solution of sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure,  
25 and the residue was purified with column chromatography (ethyl acetate/hexane=1:1) and recrystallized from ethyl acetate/hexane to give pale yellow crystals of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (827mg).  
30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.11 (2H, t, J=6.5 Hz), 3.62 (2H, t, J=6.5 Hz), 3.87 (3H, s), 7.64-7.76 (3H, m), 8.03 (1H, d, J=8.4 Hz).  
IR (KBr) 1718, 1288, 1263, 1165, 1128, 1090, 797, 748 cm<sup>-1</sup>  
Anal. for C<sub>12</sub>H<sub>11</sub>O<sub>4</sub>SBr  
35 Calcd. C, 43.52 ; H, 3.35  
Found. C, 43.39 ; H, 3.38.

## Reference Example 3

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.7g), 4-morpholinophenyl borate (481mg) and  
5 potassium carbonate (0.59g) in toluene/ethanol/water (20/2/2ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed for 20 hours and cooled.

To the mixture was added water, and the mixture was  
10 extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and precipitated solid was recrystallized from ethyl acetate/hexane to give yellow  
15 crystals of methyl 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (617.6mg).

m.p. 215-217 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.10-3.17 (2H, m), 3.23-3.28 (4H, m),  
3.61-3.67 (2H, m), 3.87 (3H, s), 3.84-3.95 (4H, m), 7.00  
(2H, d, J=8.8 Hz), 7.56 (2H, d, J=8.8 Hz), 7.66-7.74 (2H,  
20 m), 7.91 (1H, s), 8.18 (1H, d, J=8.8 Hz).

IR (KBr) 1705, 1605, 1520, 1309, 1290, 1238, 1165, 1126,  
928, 816, 752 cm<sup>-1</sup>

Anal. for C<sub>22</sub>H<sub>23</sub>NO<sub>5</sub>S

Calcd. C, 63.90 ; H, 5.61 ; N, 3.39

25 Found. C, 63.89 ; H, 5.74 ; N, 3.51.

## Reference Example 4

To a solution of methyl 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (550mg) in ethanol/THF (15ml/15ml) was added at room  
30 temperature 1N sodium hydroxide solution (1.6ml), and the mixture was stirred for 18 hours. To the mixture was added 1N hydrochloric acid (1.6ml), and the mixture was concentrated under reduced pressure. Precipitated  
crystals were collected by filtration and washed with  
35 2-propanol and diethylether to give yellow crystals of 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-

benzothiepine-4-carboxylic acid (268.9mg). The mother liquor was concentrated, and the resulting solid was collected by filtration (177mg). (Second crystals, Purity: about 50%)

5  $^1\text{H-NMR}$  (200MHz, DMSO- $d_6$ )  $\delta$  2.89-3.02 (2H, m), 3.15-3.26 (4H, m), 3.68-3.82 (6H, m), 7.06 (2H, d,  $J=9.0$  Hz), 7.74 (2H, d,  $J=9.0$  Hz), 7.83-7.91 (2H, m), 7.99-8.08 (2H, m).  
IR (KBr) 3408, 1711, 1678, 1605, 1520, 1290, 1236, 1167, 1124, 928, 820, 746  $\text{cm}^{-1}$

10 Anal. for  $\text{C}_{21}\text{H}_{21}\text{NO}_5\text{S}\cdot 0.5\text{H}_2\text{O}$

Calcd. C, 61.75 ; H, 5.43 ; N, 3.43

Found. C, 61.60 ; H, 5.65 ; N, 3.50.

Reference Example 5

A mixture of methyl 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (100mg) and 6N hydrochloric acid (10ml) was stirred at 70°C for 4 hours and concentrated under reduced pressure. To the residue was added 2-propanol, and the resulting solid was collected by filtration and washed with 2-propanol and diethylether to give yellow powder of 7-(4-morpholinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid hydrochloride (89.3mg).  
15  $^1\text{H-NMR}$  (200MHz, DMSO- $d_6$ )  $\delta$  2.89-3.02 (2H, m), 3.15-3.26 (4H, m), 3.68-3.82 (4H, m), 7.06 (2H, d,  $J=9.0$  Hz), 7.74 (2H, d,  $J=9.0$  Hz), 7.83-7.91 (2H, m), 7.99-8.08 (2H, m).  
20 Anal. for  $\text{C}_{21}\text{H}_{21}\text{NO}_5\text{S}\cdot \text{HCl}$

Calcd. C, 57.86 ; H, 5.09 ; N, 3.21

Found. C, 57.47 ; H, 5.12 ; N, 3.31.

Reference Example 6

30 To a solution of methyl 7-(4-methoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (0.60g) in THF (10ml) was added at 0°C 70% 3-chloroperbenzoic acid (1.0g), and the mixture was stirred at 0°C for 30 minutes and then at room temperature for 2 hours. To the mixture was added  
35 an aqueous solution of sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with



dichloromethane. The organic layer was washed with sodium bicarbonate solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give solid, which was recrystallized from ethyl acetate/hexane to give colorless crystals of methyl 7-(4-methoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (584.5mg).  
m.p. 191-193 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.11-3.17 (2H, m), 3.61-3.68 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 7.02 (2H, d, J=9.0 Hz), 7.57 (2H, d, J=9.0 Hz), 7.66-7.70 (2H, m), 7.92 (1H, s), 8.20 (1H, d, J=8.6 Hz).

IR (KBr) 1713, 1603, 1516, 1437, 1286, 1248, 1171, 1128, 1030, 820, 750, 606 cm<sup>-1</sup>

Anal. for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>S

Calcd. C, 63.67 ; H, 5.06

Found. C, 63.88 ; H, 5.14.

#### Reference Example 7

To a solution of methyl 7-(4-methoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (463mg) in 1,2-dimethoxyethane (30ml) was added 6N hydrochloric acid (30ml), and the mixture was refluxed for 18 hours and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals washed with 2-propanol and hexane to give pale yellow crystals of 7-(4-methoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (384mg).  
m.p. 250 °C (dec.)

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.91-3.01 (2H, m), 3.71-3.78 (2H, m), 3.83 (3H, s), 7.08 (2H, d, J=8.8 Hz), 7.80 (2H, d, J=8.8 Hz), 7.84-7.91 (2H, m), 8.03-8.07 (2H, m).

IR (KBr) 2978, 1682, 1608, 1520, 1292, 1255, 1165, 1130, 824 cm<sup>-1</sup>

Anal. for C<sub>18</sub>H<sub>16</sub>O<sub>5</sub>S

Calcd. C, 62.78 ; H, 4.68

Found. C, 62.51 ; H, 4.50.

## Reference Example 8

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-ethoxyphenyl borate (0.44g) and potassium carbonate (0.67g) in toluene/ethanol/water (20/2/2ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 16 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The resulting solid was recrystallized from ethyl acetate/hexane to give pale yellow crystals of methyl 7-(4-ethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (739.5mg).

m.p. 173-175 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.46 (3H, t, J=7.0 Hz), 3.11-3.17 (2H, m), 3.61-3.68 (2H, m), 3.87 (3H, s), 4.10 (2H, q, J=7.0 Hz), 7.00 (2H, d, J=8.8 Hz), 7.55 (2H, d, J=8.8 Hz), 7.64-7.72 (2H, m), 7.91 (1H, s), 8.19 (1H, d, J=8.4 Hz).

IR (KBr) 1713, 1608, 1518, 1292, 1250, 1225, 1167, 1132, 1038, 829, 757 cm<sup>-1</sup>

Anal. for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>S

Calcd. C, 64.50 ; H, 5.41

Found. C, 64.21 ; H, 5.26.

## Reference Example 9

To a solution of methyl 7-(4-ethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (600mg) in 1,2-dimethoxyethane (40ml) was added 6N hydrochloric acid (30ml), and the mixture was refluxed for 7 hours and concentrated under reduced pressure. To the residue was added 2-propanol, and precipitated crystals were collected by filtration. The crystals were dissolved in THF, and the solution was concentrated to give crystals, which were collected by filtration to give pale yellow crystals of 7-(4-ethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (507.5mg).

m.p. 278 °C (dec.)

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.36 (3H, t, J=7.0 Hz), 2.94-3.00 (2H, m), 3.71-3.78 (2H, m), 4.10 (2H, q, J=7.0 Hz), 7.06 (2H, d, J=8.8 Hz), 7.78 (2H, d, J=8.8 Hz), 7.83-7.92 (2H, m), 8.03-8.07 (2H, m).

IR (KBr) 3039, 1676, 1608, 1518, 1294, 1250, 1165, 1130, 827, 746 cm<sup>-1</sup>

Anal. for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>S

Calcd. C, 63.67 ; H, 5.06

Found. C, 63.73 ; H, 5.28.

Reference Example 10

To a solution of methyl 7-(3,4-methylenedioxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g) in THF (10ml) was added at 0°C 70% 3-chloroperbenzoic acid (1.22g), and the mixture was stirred at 0°C for 15 minutes and then at room temperature for 2 hours.

To the mixture was added an aqueous solution of sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with dichloromethane. The organic layer was washed with sodium bicarbonate solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give solid, which was recrystallized from THF/isopropanol to give colorless crystals of methyl 7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (763.3mg).

m.p. 185-187 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.11-3.17 (2H, m), 3.61-3.65 (2H, m), 3.87 (3H, s), 6.05 (2H, s), 6.92 (1H, dd, J=7.3, 1.1 Hz), 7.08-7.13 (2H, m), 7.62-7.66 (2H, m), 7.90 (1H, br s), 8.20 (1H, d, J=8.8 Hz).

IR (KBr) 1714, 1481, 1277, 1252, 1232, 1130, 1036, 804, 754 cm<sup>-1</sup>

Anal. for C<sub>19</sub>H<sub>16</sub>O<sub>6</sub>S

Calcd. C, 61.28 ; H, 4.33

Found. C, 61.41 ; H, 4.56.

Reference Example 11

- To a solution of methyl 7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (500mg) in 1,2-dimethoxyethane (50ml) was added 6N hydrochloric acid (30ml), and the mixture was refluxed for 5 hours and concentrated under reduced pressure. Precipitates were collected by filtration and washed with 2-propanol and diethylether to give pale yellow crystals of 7-(3,4-methylenedioxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (415.7mg).
- m.p. 254 °C (dec.)
- <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.97 (2H, t, J=6.6 Hz), 3.71-3.78 (2H, m), 6.10 (2H, s), 7.05 (1H, d, J=8.0 Hz), 7.34 (1H, dd, J=8.0, 1.8 Hz), 7.50 (1H, d, J=1.8 Hz), 7.82-7.90 (2H, m), 8.01-8.06 (2H, m).
- IR (KBr) 3439, 1678, 1479, 1290, 1234, 1128, 1038 cm<sup>-1</sup>
- Anal. for C<sub>18</sub>H<sub>14</sub>O<sub>6</sub>S·0.2H<sub>2</sub>O
- Calcd. C, 59.73 ; H, 4.01
- Found. C, 59.82 ; H, 3.95.

Reference Example 12

- Under argon atmosphere, methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.70g), a mixture of 4-chlorophenyl borate (0.38g) and potassium carbonate (0.59g) in toluene/ethanol/water (20/2/2ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed for 20 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.
- The residue was purified with column chromatography (ethyl acetate/hexane=1:1) and recrystallized from ethyl acetate/hexane to give pale yellow crystals of methyl 7-(4-chlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (466mg).
- m.p. 168-170 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.15 (2H, t, J=6.2 Hz), 3.62-3.68 (2H,

m), 3.88 (3H, s), 7.44-7.57 (4H, m), 7.67-7.70 (2H, m), 7.91 (1H, s), 8.24 (1H, d, J=8.6 Hz).

IR (KBr) 1720, 1296, 1275, 1248, 1223, 1194, 1165, 1132, 1090, 822, 752  $\text{cm}^{-1}$

5 Anal. for  $\text{C}_{18}\text{H}_{15}\text{O}_4\text{SCl}$

Calcd. C, 59.59 ; H, 4.17

Found. C, 59.77 ; H, 4.14.

Reference Example 13

To a solution of methyl 7-(4-chlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.95g)  
10 in 1,2-dimethoxyethane (50ml) was added 6N hydrochloric acid (30ml), and the mixture was stirred at 70°C for 64 hours.

The mixture was cooled to room temperature, extracted with ethyl acetate, saturated brine, dried with magnesium sulfate  
15 and concentrated under reduced pressure. Precipitated crystals were collected by filtration, and the crystals was washed with diisopropylether and hexane to give pale yellow crystals of 7-(4-chlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (804.9mg).

20 m.p. 288 °C (dec.)

$^1\text{H-NMR}$  (200MHz,  $\text{DMSO-d}_6$ )  $\delta$  2.95-3.01 (2H, m), 3.73-3.80 (2H, m), 7.59 (2H, d, J=8.4 Hz), 7.85-7.96 (4H, m), 8.10 (1H, d, J=8.0 Hz), 8.14 (1H, s).

IR (KBr) 2987, 1697, 1142, 1294, 1165, 1134, 1093, 818  $\text{cm}^{-1}$

25 Anal. for  $\text{C}_{17}\text{H}_{13}\text{O}_4\text{SCl}$

Calcd. C, 58.54 ; H, 3.76

Found. C, 58.55 ; H, 3.85.

Reference Example 14

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.0g), 4-fluorophenyl borate (0.465g) and potassium carbonate (0.84g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To  
30 the mixture was added tetrakis(triphenylphosphine)palladium (0.17g), and the mixture was refluxed for 20 hours, cooled, extracted with ethyl acetate, saturated brine, dried with  
35

magnesium sulfate and concentrated under reduced pressure.

The residue was purified with column chromatography (ethyl acetate/hexane=1:1) and recrystallized from ethyl acetate/hexane=1:1 to give pale yellow crystals of methyl

5 7-(4-fluorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (656.3mg).

m.p. 180-183 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.12-3.19 (2H, m), 3.62-3.69 (2H, m), 3.88 (3H, s), 7.15-7.24 (2H, m), 7.55-7.70 (4H, m), 7.91 (1H, br s), 8.23 (1H, d, J=9.2 Hz).

10 IR (KBr) 1718, 1692, 1514, 1279, 1242, 1201, 1161, 1130, 831, 752, 604, 519 cm<sup>-1</sup>

Anal. for C<sub>18</sub>H<sub>15</sub>O<sub>4</sub>SF

Calcd. C, 62.42 ; H, 4.36

15 Found. C, 62.38 ; H, 4.40.

Reference Example 15

To a solution of methyl 7-(4-fluorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.55g) in 1,2-dimethoxyethane (20ml) was added 6N hydrochloric acid (10ml), and the mixture was refluxed for 29 hours, cooled to room temperature, extracted with ethyl acetate, saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with diisopropylether and hexane to give pale yellow crystals of 7-(4-fluorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (490.7mg).

m.p. 260 °C (dec.)

30 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.98 (2H, t, J=7.0 Hz), 3.76 (2H, d, J=7.0 Hz), 7.32-7.40 (2H, m), 7.85-7.94 (4H, m), 8.07-8.11 (2H, m).

IR (KBr) 2939, 1687, 1514, 1296, 1161, 1132, 824 cm<sup>-1</sup>

Anal. for C<sub>17</sub>H<sub>13</sub>O<sub>4</sub>SF

Calcd. C, 61.44 ; H, 3.94

35 Found. C, 61.20 ; H, 4.09.

Reference Example 16

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.00g), 4-trifluoromethylphenyl borate (0.63g) and potassium carbonate (0.84g) in 5 toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.174g), and the mixture was refluxed for 16 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with 10 magnesium sulfate and concentrated under reduced pressure.

The residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give pale yellow crystals of methyl 7-(4-trifluoromethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (704.7mg).

15 m.p. 168-170 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.13-3.20 (2H, m), 3.63-3.70 (2H, m), 3.88 (3H, s), 7.67-7.80 (6H, m), 7.92 (1H, br s), 8.28 (1H, d, J=8.4 Hz).

IR (KBr) 1714, 1325, 1248, 1169, 1130, 1070, 831, 750 cm<sup>-1</sup>

20 Anal. for C<sub>19</sub>H<sub>15</sub>O<sub>4</sub>SF<sub>3</sub>

Calcd. C, 57.57 ; H, 3.81

Found. C, 57.62 ; H, 3.66.

Reference Example 17

To a solution of methyl 7-(4-trifluoromethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (600mg) in 1,2-dimethoxyethane (40ml) was added at room temperature 6N hydrochloric acid (20ml), and the mixture was refluxed for 22 hours, cooled to room temperature and extracted with ethyl 30 acetate/THF. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with hexane to give 35 colorless crystals of 7-(4-trifluoromethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (439.5mg).

m.p. >300 °C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.96-3.02 (2H, m), 3.75-3.82 (2H, m), 7.87-8.17 (7H, m), 8.22 (1H, d, J=1.6 Hz).

IR (KBr) 2985, 1695, 1325, 1294, 1171, 1132, 1117, 1072,  
5 829 cm<sup>-1</sup>

Anal. for C<sub>18</sub>H<sub>13</sub>O<sub>4</sub>SF<sub>3</sub>

Calcd. C, 56.54 ; H, 3.43

Found. C, 56.43 ; H, 3.55.

Reference Example 18

10 Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-ethylphenyl borate (0.40g) and  
potassium carbonate (0.67g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To  
15 the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 15 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with column  
20 chromatography (ethyl acetate/hexane=1:1) to give pale yellow crystals of methyl 7-(4-ethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (732mg).

m.p. 173-176 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.29 (3H, t, J=7.5 Hz), 2.72 (2H, q, J=7.5 Hz), 3.11-3.18 (2H, m), 3.62-3.68 (2H, m), 3.87 (3H, s), 7.33 (2H, d, J=8.1 Hz), 7.54 (2H, d, J=8.1 Hz), 7.66-7.74 (2H, m), 7.92 (1H, br s), 8.21 (1H, d, J=8.4 Hz).

IR (KBr) 1714, 1315, 1294, 1277, 1252, 1223, 1165, 1130, 825, 750 cm<sup>-1</sup>

30 Anal. for C<sub>20</sub>H<sub>20</sub>O<sub>4</sub>S

Calcd. C, 67.39 ; H, 5.66

Found. C, 67.36 ; H, 5.63.

Reference Example 19

To a solution of methyl 7-(4-ethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (600mg)  
35 in 1,2-dimethoxyethane (20ml) was added 6N hydrochloric acid



(10ml), and the mixture was refluxed for 24 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with hexane to give pale yellow crystals of 7-(4-ethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (501.2mg).  
m.p. 260-265 °C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.29 (3H, t, J=7.6 Hz), 2.73 (2H, q, J=7.6 Hz), 3.17 (2H, t, J=6.6 Hz), 3.67 (2H, t, J=6.6 Hz), 7.34 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.70-7.78 (2H, m), 8.02 (1H, s), 8.24 (1H, d, J=8.8 Hz).  
IR (KBr) 2966, 1675, 1290, 1163, 1128, 824, 744 cm<sup>-1</sup>

Anal. for C<sub>19</sub>H<sub>18</sub>O<sub>4</sub>S  
Calcd. C, 66.65 ; H, 5.30  
Found. C, 66.47 ; H, 5.41.  
Reference Example 20

Under argon atmosphere, a mixture of methyl 7-bromo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-isopropylphenyl borate (0.44g) and potassium carbonate (0.67g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 20 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

The residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give pale yellow crystals of methyl 7-(4-isopropylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (774.7mg).  
m.p. 142-144 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.30 (6H, d, J=6.6 Hz), 2.90-3.06 (1H, m), 3.12-3.18 (2H, m), 3.62-3.68 (2H, m), 3.87 (3H, s), 7.36 (2H, d, J=8.2 Hz), 7.55 (2H, d, J=8.2 Hz), 7.69-7.73 (2H, m), 7.92 (1H, br s), 8.22 (1H, d, J=8.8 Hz).

IR (KBr) 1713, 1315, 1294, 1277, 1252, 1223, 1196, 1167, 1130, 825, 752  $\text{cm}^{-1}$

Anal. for  $\text{C}_{21}\text{H}_{22}\text{O}_4\text{S}$

Calcd. C, 68.08 ; H, 5.99

5 Found. C, 68.04 ; H, 6.15.

#### Reference Example 21

To a solution of methyl 7-(4-isopropylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (600mg) in 1,2-dimethoxyethane (20ml) was added at room temperature  
10 6N hydrochloric acid (10ml), and the mixture was refluxed for 24 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by  
15 filtration. The crystals were washed with hexane to give colorless crystals of 7-(4-isopropylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (555.2mg). m.p. 282  $^{\circ}\text{C}$  (dec.)

$^1\text{H}$ -NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (6H, d,  $J=7.0$  Hz), 2.92-3.05 (1H, m), 3.13-3.20 (2H, m), 3.63-3.70 (2H, m), 7.36 (2H, d,  $J=8.5$  Hz), 7.56 (2H, d,  $J=8.2$  Hz), 7.69-7.78 (2H, m), 8.01 (1H, br s), 8.24 (1H, d,  $J=8.8$  Hz).

IR (KBr) 2962, 1676, 1294, 1167, 1132, 824, 748  $\text{cm}^{-1}$

Anal. for  $\text{C}_{20}\text{H}_{20}\text{O}_4\text{S} \cdot 0.2\text{H}_2\text{O}$

25 Calcd. C, 66.72 ; H, 5.71

Found. C, 66.63 ; H, 5.79.

#### Reference Example 22

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-  
30 carboxylate (0.80g), 4-tert-butylphenyl borate (0.47g) and potassium carbonate (0.67g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 16 hours, cooled,  
35 extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced

pressure. The residue was purified with column chromatography (ethyl acetate/hexane=1:1) and recrystallized from ethyl acetate/diisopropylether to give colorless crystals of methyl 7-(4-tert-butylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (793.6mg).

m.p. 170-172 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.38 (9H, s), 3.12-3.18 (2H, m), 3.62-3.69 (2H, m), 3.88 (3H, s), 7.49-7.59 (4H, m), 7.70-7.74 (2H, m), 7.92 (1H, br s), 8.22 (1H, d, J=8.8 Hz).

IR (KBr) 1713, 1319, 1296, 1277, 1244, 1198, 1169, 1128, 827, 752 cm<sup>-1</sup>

Anal. for C<sub>22</sub>H<sub>24</sub>O<sub>4</sub>S

Calcd. C, 68.72 ; H, 6.29

Found. C, 68.67 ; H, 6.31.

Reference Example 23

To a solution of methyl 7-(4-tert-butylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (400mg) in 1,2-dimethoxyethane (20ml) was added 6N hydrochloric acid (10ml), and the mixture was stirred at 70°C for 55 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and washed with hexane to give pale yellow crystals of 7-(4-tert-butylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (362.7mg).

m.p. 289-291 °C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.33 (9H, s), 2.94-3.01 (2H, m), 3.73-3.79 (2H, m), 7.54 (2H, d, J=8.6 Hz), 7.76 (2H, d, J=8.6 Hz), 7.89-7.93 (2H, m), 8.06-8.11 (2H, m).

IR (KBr) 2962, 1689, 1292, 1165, 1132, 824, 748 cm<sup>-1</sup>

Anal. for C<sub>21</sub>H<sub>22</sub>O<sub>4</sub>S

Calcd. C, 68.08 ; H, 5.99

Found. C, 67.93 ; H, 5.69.

## Reference Example 24

- Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-(1-pyrrolidinyl)phenyl borate (508mg) and potassium carbonate (0.67g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 17 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with diisopropylether to give yellow crystals of methyl 7-[4-(1-pyrrolidinyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (323mg). m.p. 227 °C (dec.)
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.00-2.11 (4H, m), 3.09-3.16 (2H, m), 3.29-3.41 (4H, m), 3.61-3.67 (2H, m), 3.87 (3H, s), 6.65 (2H, d, J=8.8 Hz), 7.54 (2H, d, J=8.8 Hz), 7.65-7.69 (2H, m), 7.91 (1H, br s), 8.15 (1H, d, J=9.2 Hz).
- IR (KBr) 1714, 1608, 1585, 1529, 1385, 1313, 1279, 1252, 1163, 1128, 808, 754 cm<sup>-1</sup>
- Anal. for C<sub>22</sub>H<sub>23</sub>NO<sub>4</sub>S  
Calcd. C, 66.48 ; H, 5.83 ; N, 3.52  
Found. C, 66.74 ; H, 5.82 ; N, 3.38.

## Reference Example 25

- To methyl 7-[4-(1-pyrrolidinyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (270mg) was added 6N hydrochloric acid (30ml), and the mixture was stirred at 70°C for 7 hours and concentrated under reduced pressure. To the residue was added 2-propanol to give crystals, which were collected by filtration. The crystals were washed with 2-propanol and hexane to give yellow crystals of 7-[4-(1-pyrrolidinyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid hydrochloride (204mg).

m.p. 283 °C (dec.)

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.86-2.03 (4H, m), 2.95 (2H, t, J=6.3 Hz), 3.23-3.36 (4H, m), 3.69-3.75 (2H, m), 6.67 (2H, d, J=8.7 Hz), 7.70 (2H, d, J=8.7 Hz), 7.80-7.86 (2H, m), 7.97-8.01 (2H, m).

IR (KBr) 2883, 1701, 1389, 1319, 1288, 1196, 1171, 1128, 822 cm<sup>-1</sup>

Anal. for C<sub>21</sub>H<sub>22</sub>NO<sub>4</sub>SCl·0.5H<sub>2</sub>O

Calcd. C, 58.80 ; H, 5.40 ; N, 3.27

10 Found. C, 59.02 ; H, 5.27 ; N, 3.20.

Reference Example 26

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-piperidinophenyl borate (0.55g) and 15 potassium carbonate (0.67g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 15 hours, cooled, 20 extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were recrystallized from ethyl acetate to give yellow crystals of methyl 7-(4-piperidinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.85g).

25 m.p. 202-204 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.59-1.80 (6H, m), 3.10-3.16 (2H, m), 3.23-3.34 (4H, m), 3.61-3.67 (2H, m), 3.87 (3H, s), 7.01 (2H, d, J=9.0 Hz), 7.54 (2H, d, J=9.0 Hz), 7.65-7.70 (2H, m), 7.91 (1H, br s), 8.17 (1H, d, J=8.8 Hz).

30 IR (KBr) 1707, 1605, 1585, 1518, 1435, 1298, 1240, 1511, 1124, 816, 741 cm<sup>-1</sup>

Anal. for C<sub>23</sub>H<sub>25</sub>NO<sub>4</sub>S

Calcd. C, 67.13 ; H, 6.12 ; N, 3.40

Found. C, 67.12 ; H, 6.36 ; N, 3.52.

35 Reference Example 27

To methyl 7-(4-piperidinophenyl)-1,1-dioxo-2,3-

dihydro-1-benzothiepine-4-carboxylate (600mg) was added 6N hydrochloric acid (60ml), and the mixture was stirred at 70°C for 5 hours and concentrated under reduced pressure.

To the residue was added ethanol, and to the mixture were  
5 added 8N sodium hydroxide solution and 1N sodium hydroxide solution to make the solution pH 6-7. The mixture was concentrated under reduced pressure to give solid, which was collected by filtration and washed with water, 2-propanol, acetone and diisopropylether to give yellow powder  
10 of 7-(4-piperidinophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (549.5mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.45-1.60 (6H, m), 2.96 (2H, t, J=6.7 Hz), 3.12-3.46 (4H, m), 3.69-3.75 (2H, m), 7.03 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.8 Hz), 7.78-7.87 (2H, m),  
15 7.99-8.03 (2H, m).

IR (KBr) 2937, 1680, 1605, 1587, 1520, 1292, 1240, 1128, 818, 744 cm<sup>-1</sup>

#### Reference Example 28

Under argon atmosphere, A mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-trifluoromethoxyphenyl borate (0.55g) and potassium carbonate (0.67g) in  
20 toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added  
25 tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 20 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

The residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give pale yellow crystals of methyl  
30 7-(4-trifluoromethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (638.5mg).

m.p. 142-143 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.13-3.19 (2H, m), 3.62-3.69 (2H, m),  
35 3.88 (3H, s), 7.35 (2H, d, J=8.0 Hz), 7.60-7.73 (4H, m), 7.92 (1H, br s), 8.25 (1H, d, J=8.8 Hz).

IR (KBr) 1713, 1514, 1257, 1215, 1165, 1130, 837, 754  $\text{cm}^{-1}$

Anal. for  $\text{C}_{19}\text{H}_{15}\text{O}_5\text{SF}_3$

Calcd. C, 55.34 ; H, 3.67

Found. C, 55.48 ; H, 3.63.

5 Reference Example 29

To a solution of methyl 7-(4-trifluoromethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (450mg) in 1,2-dimethoxyethane (10ml) was added at room temperature 6N hydrochloric acid (5ml), and the mixture was refluxed for 24 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with hexane to give colorless crystals of 7-(4-trifluoromethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (390.3mg).

m.p. 284-285  $^{\circ}\text{C}$

20  $^1\text{H}$ -NMR (200MHz,  $\text{DMSO}-d_6$ )  $\delta$  2.95-3.02 (2H, m), 3.74-3.80 (2H, m), 7.52 (2H, d,  $J=8.0$  Hz), 7.89-7.99 (4H, m), 8.09-8.16 (2H, m).

IR (KBr) 3047, 1693, 1269, 1215, 1165, 1132  $\text{cm}^{-1}$

Anal. for  $\text{C}_{18}\text{H}_{13}\text{O}_5\text{SF}_3$

25 Calcd. C, 54.27 ; H, 3.29

Found. C, 54.22 ; H, 3.20.

Reference Example 30

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 3,4-dichlorophenyl borate (0.54g) and potassium carbonate (0.67g) in toluene/ethanol/water (30/3/3ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 18 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced

pressure. The residue was purified with column chromatography (ethyl acetate/hexane=1:2→1:1) to give pale yellow crystals of methyl 7-(3,4-dichlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (631.3mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.13-3.19 (2H, m), 3.62-3.69 (2H, m), 3.88 (3H, s), 7.45 (1H, dd, J=8.2, 2.0 Hz), 7.58 (1H, d, J=8.2 Hz), 7.66-7.71 (3H, m), 7.91 (1H, br s), 8.26 (1H, d, J=8.2 Hz).

IR (KBr) 1707, 1321, 1275, 1252, 1171, 1130, 750 cm<sup>-1</sup>  
Reference Example 31

To a solution of methyl 7-(3,4-dichlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (450mg) in 1,2-dimethoxyethane (10ml) was added 6N hydrochloric acid (10ml), and the mixture was refluxed for 64 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration to give colorless crystals of 7-(3,4-dichlorophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (395.5mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.94-3.02 (2H, m), 3.73-3.80 (2H, m), 7.78 (1H, d, J=8.4 Hz), 7.83-7.91 (2H, m), 7.97-8.02 (1H, m), 8.10 (1H, d, J=8.0 Hz), 8.18 (1H, d, J=2.2 Hz), 8.23-8.27 (1H, m).

IR (KBr) 2985, 1672, 1468, 1415, 1319, 1292, 1173, 1133, 820 cm<sup>-1</sup>

Reference Example 32

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-propylphenyl borate (0.435g) and potassium carbonate (0.67g) in toluene/ethanol/water (25/2.5/2.5ml) was stirred at room temperature for 1 hour.

To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the



mixture was refluxed for 18 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

Precipitated crystals were collected by filtration, and the  
5 crystals were washed with ethyl acetate, diisopropylether and hexane to give colorless crystals of methyl 7-(4-propylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (557.2mg).

m.p. 155-156 °C

10 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.98 (3H, t, J=7.4 Hz), 1.63-1.77 (2H, m), 2.66 (2H, t, J=7.6 Hz), 3.11-3.18 (2H, m), 3.61-3.68 (2H, m), 3.87 (3H, s), 7.30 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz), 7.69-7.73 (2H, m), 7.92 (1H, br s), 8.22 (1H, d, J=8.8 Hz).

15 IR (KBr) 1709, 1313, 1290, 1248, 1165, 1130, 748 cm<sup>-1</sup>

Anal. for C<sub>21</sub>H<sub>22</sub>O<sub>4</sub>S

Calcd. C, 68.08 ; H, 5.99

Found. C, 68.13 ; H, 5.89.

Reference Example 33

20 To a solution of methyl 7-(4-propylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (450mg) in 1,2-dimethoxyethane (15ml) was added 6N hydrochloric acid (7.5ml), and the mixture was refluxed for 40 hours, cooled to room temperature and extracted with ethyl acetate. The  
25 organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and recrystallized from THF/diisopropylether to give colorless crystals of 7-(4-propylphenyl)-1,1-dioxo-2,3-dihydro-1-  
30 benzothiepine-4-carboxylic acid (433.6mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.92 (3H, t, J=7.3 Hz), 1.58-1.69 (2H, m), 2.58-2.66 (2H, m), 2.93-3.01 (2H, m), 3.72-3.79 (2H, m), 7.34 (2H, d, J=8.2 Hz), 7.74 (2H, d, J=8.2 Hz), 7.88-7.93 (2H, m), 8.06-8.09 (2H, m).

35 IR (KBr) 3012, 1678, 1408, 1321, 1298, 1167, 1132 cm<sup>-1</sup>

Reference Example 34

- Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.80g), 4-isopropoxyphenyl borate (0.48g) and potassium carbonate (0.67g) in toluene/ethanol/water (25/2.5/2.5ml) was stirred at room temperature for 1 hour.
- To the mixture was added tetrakis(triphenylphosphine)palladium (0.14g), and the mixture was refluxed for 13 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.
- The residue was purified with column chromatography (ethyl acetate/hexane=1:2) to give colorless crystals of methyl 7-(4-isopropoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (606.5mg).
- m.p. 140-142 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.38 (6H, d, J=6.2 Hz), 3.11-3.17 (2H, m), 3.61-3.68 (2H, m), 3.87 (3H, s), 4.57-4.69 (1H, m), 6.99 (2H, d, J=9.0 Hz), 7.54 (2H, d, J=9.0 Hz), 7.66-7.70 (2H, m), 7.91 (1H, br s), 8.19 (1H, d, J=8.8 Hz).
- IR (KBr) 1709, 1516, 1309, 1288, 1246, 1165, 1128, 829, 750 cm<sup>-1</sup>
- Anal. for C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>S
- Calcd. C, 65.27 ; H, 5.74
- Found. C, 65.13 ; H, 5.83.
- Reference Example 35
- To a solution of methyl 7-(4-isopropoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (250mg) in 1,2-dimethoxyethane (10ml) was added 6N hydrochloric acid (3ml), and the mixture was stirred at 70°C for 18 hours. To the mixture were added 1,2-dimethoxyethane (10ml) and 6N hydrochloric acid (5ml), and the mixture was stirred at 70°C for 4 days, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with

hexane to give colorless crystals of 7-(4-isopropoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (230.3mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.30 (6H, d, J=5.8 Hz), 2.93-3.00 (2H, m), 3.71 (2H, m), 4.63-4.78 (1H, m), 7.04 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.84-7.91 (2H, m), 8.03-8.07 (2H, m).

IR (KBr) 2977, 1676, 1608, 1513, 1292, 1246, 1165, 1130, 951, 829, 746 cm<sup>-1</sup>

10 Reference Example 36

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.70g), 4-propoxyphenyl borate (0.38g) and potassium carbonate (0.58g) in toluene/ethanol/water (20/2/2ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed for 18 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (ethyl acetate/hexane=1:2→1:1) to give pale yellow crystals of methyl 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (616.4mg).

25 m.p. 153-155 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.07 (3H, t, J=7.5 Hz), 1.76-1.93 (2H, m), 3.11-3.17 (2H, m), 3.61-3.68 (2H, m), 3.87 (3H, s), 3.99 (2H, t, J=6.6 Hz), 7.01 (2H, d, J=9.0 Hz), 7.55 (2H, d, J=9.0 Hz), 7.66-7.70 (2H, m), 7.91 (1H, br s), 8.20 (1H, d, J=8.4 Hz).

30 IR (KBr) 1718, 1608, 1518, 1315, 1281, 1248, 1223, 1163, 1132, 831, 754 cm<sup>-1</sup>

Anal. for C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>S

Calcd. C, 65.27 ; H, 5.74

35 Found. C, 65.35 ; H, 5.63.

Reference Example 37

To a solution of methyl 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (400mg) in 1,2-dimethoxyethane (10ml) was added 6N hydrochloric acid (5ml), and the mixture was refluxed for 2 days, cooled to room temperature and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with water, 2-propanol and diisopropylether to give colorless crystals of 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (346.1mg).

m.p. 270-273 °C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.00 (3H, t, J=7.5 Hz), 1.65-1.86 (2H, m), 2.93-3.00 (2H, m), 3.71-3.78 (2H, m), 4.00 (2H, t, J=6.6 Hz), 7.06 (2H, d, J=8.7 Hz), 7.78 (2H, d, J=8.7 Hz), 7.83-7.93 (2H, m), 8.03-8.07 (2H, m).

IR (KBr) 2972, 1676, 1608, 1518, 1292, 1250, 1163, 1128, 827, 746 cm<sup>-1</sup>

Anal. for C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>S

Calcd. C, 64.50 ; H, 5.41

Found. C, 64.34 ; H, 5.48.

Reference Example 38

Under argon atmosphere, a mixture of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (0.70g), 4-butoxyphenyl borate (0.45g) and potassium carbonate (0.58g) in toluene/ethanol/water (20/2/2ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed for 20 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with column chromatography (ethyl acetate/hexane=1:1) to give colorless crystals of methyl 7-(4-butoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (672.6mg).

m.p. 123-125 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.00 (3H, t, J=7.1 Hz), 1.45-1.62 (2H, m), 1.74-1.88 (2H, m), 3.11-3.18 (2H, m), 3.61-3.68 (2H, m), 3.87 (3H, s), 4.03 (2H, t, J=6.4 Hz), 7.01 (2H, d, J=8.8 Hz), 7.55 (2H, d, J=8.8 Hz), 7.64-7.72 (2H, m), 7.91 (1H, br 2), 8.19 (1H, d, J=8.8 Hz).

IR (KBr) 1714, 1516, 1317, 1294, 1248, 1223, 1165, 1132, 824, 750 cm<sup>-1</sup>

Anal. for C<sub>22</sub>H<sub>24</sub>O<sub>5</sub>S

Calcd. C, 65.98 ; H, 6.04

10 Found. C, 66.27 ; H, 5.78.

Reference Example 39

To a solution of methyl 7-(4-butoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (500mg) in 1,2-dimethoxyethane (10ml) was added 6N hydrochloric acid (5ml), and the mixture was refluxed for 16 hours. To the mixture were added 1,2-dimethoxyethane (5ml) and 6N hydrochloric acid (2ml), and the mixture was refluxed for 4 hours, cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration. The crystals were washed with diisopropylether to give colorless crystals of 7-(4-butoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (388.9mg).

m.p. 244-247 °C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.95 (3H, t, J=7.1 Hz), 1.35-1.56 (2H, m), 1.64-1.81 (2H, m), 2.93-3.00 (2H, m), 3.71-3.78 (2H, m), 4.04 (2H, t, J=6.6 Hz), 7.06 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.8 Hz), 7.85-7.90 (2H, m), 8.03-8.07 (2H, m).

IR (KBr) 2958, 1676, 1608, 1518, 1408, 1292, 1252, 1163, 1128, 827, 746 cm<sup>-1</sup>

Anal. for C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>S

35 Calcd. C, 65.27 ; H, 5.74

Found. C, 65.28 ; H, 5.70.

## Reference Example 40

To a solution of ethyl 6-(4-methylphenyl)-1,2-dihydro-2H-thiochromene-3-carboxylate (1.03 g, 3.32 mmol) in dichloromethane (20 ml) was added at 0°C m-chloroperbenzoic acid (1.73 g, 6.98 mmol), and the mixture was stirred for 20 minutes and then at room temperature for 20 minutes. The mixture was neutralized with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic layer was dried with magnesium sulfate, and the solvent was evaporated to give colorless powder, which was washed with ethanol to give ethyl 6-(4-methylphenyl)-1,1-dioxo-1,2-dihydro-2H-thiochromene-3-carboxylate (0.95 g, 84%). A part of the product was recrystallized from ethyl acetate to give colorless flake crystals.

m.p. 174°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 8.09 (1H, d, J=8.0), 7.87 (1H, s), 7.80 (1H, dd, J=8.0, 1.8), 7.70 (1H, d, J=1.8), 7.41 (2H, d, J=8.0), 7.31 (2H, d, J=8.0), 4.35 (2H, q, J=7.4), 4.29 (2H, d, J=1.8), 2.43 (3H, s), 1.39 (3H, t, J=7.4).

Anal. Calcd for C<sub>19</sub>H<sub>16</sub>O<sub>4</sub>S · 0.25H<sub>2</sub>O: C; 65.78, H; 5.37.

Found: C; 65.93, H; 5.26.

## Reference Example 41

To a solution of ethyl 6-(4-methylphenyl)-1,1-dioxo-1,2-dihydro-2H-thiochromene-3-carboxylate (0.90g, 2.63 mmol) in tetrahydrofuran (10 ml) and acetonitrile (10 ml) was added dropwise 1N sodium hydroxide (3 ml), and the mixture was stirred for 1 hour. The reaction solution was distributed to diethylether and water, and the aqueous layer was made pH 3 with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated to give crude carboxylic acid as brown powder, which was washed with ethanol to give 6-(4-methylphenyl)-1,1-dioxo-1,2-dihydro-2H-thiochromene-3-carboxylic acid (0.24g, 29%) as pale yellow powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.95-7.99 (3H, m), 7.69 (2H, d, J=8.2), 7.35 (2H, d, J=8.2), 4.45 (2H, s), 3.78 (3H, s).

Reference Example 42

To a solution of methyl 7-(4-methylphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (1.5g) in dichloromethane (25ml) was added, under ice-cooling, 70% mCPBA (2.4g), and the mixture was stirred at room temperature for 1 hour. To the solution was added an aqueous solution of sodium thiosulfate, and the mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give methyl 7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.6g) as colorless crystals. mp 203-204°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.43 (3H, s), 3.15 (2H, t, J=6.6Hz), 3.65 (2H, t, J=6.6Hz), 3.88 (3H, s), 7.31 (2H, d, J=8.3Hz), 7.52 (2H, d, J=8.3Hz), 7.69-7.74 (2H, m), 7.92 (1H, s), 8.22 (1H, d, J=8.8Hz).

IR(KBr) ν: 2951, 1713cm<sup>-1</sup>.

Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>O<sub>4</sub>S: C, 66.65; H, 5.30.

Found C, 66.47; H, 5.33.

Reference Example 43

To methyl 7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (1.6g) was added 1N sodium hydroxide solution (50ml), methanol (200ml) and diethylether (100ml), and the mixture was stirred overnight, concentrated and extracted with water. The aqueous layer was washed with ethyl acetate, made acidic with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-(4-methylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (1.5g; purity about 70%) as colorless powder.

<sup>1</sup>H-NMR(  $\delta$  ppm, CDCl<sub>3</sub>) 2.43 (3H, s), 3.14 (2H, t, J=6.6Hz), 3.66 (2H, t, J=6.6Hz), 7.26-7.33 (2H, m), 7.47-7.57 (2H, m), 7.70-7.74 (2H, m), 7.95 (1H, s), 8.21 (1H, d, J=8.8Hz).

Reference Example 44

- 5 In toluene/ethanol/water (10/1/1.2ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (870mg), and to the solution were added 5-methyl-2-thienyl borate (530mg) and potassium carbonate (1.02g). The mixture was stirred at room temperature for
- 10 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (152mg). The mixture was stirred at 100°C for 16 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure,
- 15 the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=3/1) to give methyl 7-(5-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (210mg). <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>)  $\delta$  2.54 (3H, d, J=1.0Hz), 3.12 (2H, m),
- 20 3.63 (2H, m), 3.89 (3H, s), 6.79 (1H, dd, J=3.6, 1.0Hz), 7.26 (1H, d, J=3.6Hz), 7.61-7.66 (2H, m), 7.86 (1H, s), 8.12 (1H, d, J=8.8Hz)

Reference Example 45

- 25 In 1,2-dimethoxyethane (10.5ml) was dissolved methyl 7-(5-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (210mg), and to the solution was added 6N hydrochloric acid (6.3ml). The mixture was stirred at 100°C for 14 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine
- 30 and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-(5-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (180mg).
- 35 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$  2.49 (3H, s), 2.93 (2H, m), 3.72 (2H, m), 6.89 (1H, d, J=3.6Hz), 7.59 (1H, d, J=3.6Hz), 7.72-7.81 (2H, m), 8.05 (1H, s), 7.98 (2H, d, J=8.0Hz)



## Reference Example 46

In toluene/ethanol/water (10/1/1.2ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (800mg), and to the solution were added 4-methyl-2-thienyl borate (524mg) and potassium carbonate (935mg). The mixture was stirred at room temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (152mg). The mixture was stirred at 100°C for 16 hours and cooled to room temperature. To the mixture was added water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=3/1) to give methyl 7-(4-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (510mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.31 (3H, m), 3.09 (2H, m), 3.63 (2H, t, J=6.6Hz), 3.87 (3H, s), 7.00 (1H, m), 7.27 (1H, m), 7.64-7.70 (2H, m), 7.86 (1H, s), 8.13 (1H, d, J=10.8Hz)

## Reference Example 47

In 1,2-dimethoxyethane (15.3ml) was dissolved methyl 7-(4-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (510mg), and to the solution was added 6N hydrochloric acid (10.2ml). The mixture was stirred at 100°C for 15 hours and cooled to room temperature.

Under reduced pressure, the solvent was evaporated. To the residue were added ethyl acetate and potassium carbonate solution, and the mixture was extracted with water. To the solution was added 6N hydrochloric acid, and the solution was made pH 4-5, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-(4-methyl-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (459mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.51 (3H, s), 2.95 (2H, t, J=6.6Hz),

3.74 (2H, t, J=6.6Hz), 6.91 (1H, d, J=3.6Hz), 7.61 (1H, d, J=3.6Hz), 7.73-7.94 (2H, m), 8.05 (1H, s), 8.00 (2H, d, J=8.4Hz)

Reference Example 48

5 In toluene/ethanol/water (10/1/1.2ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (750mg), and to the solution were added 5-chloro-2-thienyl borate (736mg) and potassium carbonate (1.0g). The mixture was stirred at room temperature for 30  
10 minutes, and to the mixture was added tetrakis(triphenyl)phosphinepalladium (210mg). The mixture was stirred at 100°C for 15 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure,  
15 the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate = 3/1) to give methyl 7-(5-chloro-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (350mg).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.13 (2H, m), 3.64 (2H, t, m), 3.87  
20 (3H, s), 3.88 (3H, s), 6.98 (1H, d, J=4.2Hz), 7.44 (1H, d, J=4.2Hz), 7.60-7.64 (2H, m), 7.86 (1H, s), 8.17 (1H, d, J=8.6Hz)

Reference Example 49

In 1,2-dimethoxyethane (11.5ml) was dissolved methyl  
25 7-(5-chloro-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (230mg), and to the mixture was added 6N hydrochloric acid (9.2ml). The mixture was stirred at 100°C for 16 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried  
30 with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-(5-chloro-2-thienyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.96 (2H, m), 3.75 (2H, t, m), 7.25  
35 (2H, d, J=4.0Hz), 7.70 (2H, d, J=4.0Hz), 7.79-7.84 (2H, m), 8.03 (1H, d, J=8.4Hz), 8.09 (1H, s)

## Reference Example 50

In toluene (21.7ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (900mg), and to the solution was added

5 tetrakis(triphenylphosphine)palladium (243mg). The mixture was stirred for 15 minutes, and to the mixture were added 4-(methylthio)phenyl borate (1.82g), 2N sodium carbonate (2.7ml) and methanol (5.4ml). The mixture was stirred at 75°C for 4 hours, cooled to room temperature, extracted with

10 ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was concentrated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give methyl 7-[(4-methylthio)phenyl]-1,1-dioxo-2,3-dihydro-

15 1-benzothiepine-4-carboxylate (340mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.55 (3H, s), 2.97 (2H, m), 3.75 (2H, m), 7.39 (2H, d, J=8.6Hz), 7.79 (2H, d, J=8.6Hz), 7.91 (2H, d, J=8.6Hz), 8.05 (1H, s), 8.10 (1H, d, J=9.8Hz)

## Reference Example 51

20 In 1,2-dimethoxyethane (10ml) and 6N hydrochloric acid (10ml) was dissolved methyl 7-[(4-methylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (330mg), and the mixture was stirred at 100°C for 18 hours, cooled to room temperature, extracted with ethyl acetate,

25 washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-[(4-methylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (133mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.54 (3H, s), 3.06 (2H, q, J=7.4Hz), 3.75 (2H, t, J=6.4Hz), 7.43 (2H, d, J=8.4Hz), 7.79 (2H, d, J=8.4Hz), 7.89-7.95 (2H, m), 8.06-8.12 (2H, m)

30

## Reference Example 52

In toluene/ethanol/water (10/1/1.2ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-

35 carboxylate (1.16g), and to the solution were added 4-(ethylthio)phenyl borate (1.28g) and potassium carbonate

(1.45g). The mixture was stirred at room temperature for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (243mg). The mixture was stirred at 100°C for 20 hours, cooled to room temperature, 5 extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ ethyl acetate=2/1) to give methyl 7-[(4-ethylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate 10 (330mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.37 (3H, t, J=7.4Hz), 3.02 (2H, q, J=7.4Hz), 3.15 (2H, m), 3.65 (2H, m), 3.87 (3H, s), 7.40 (2H, m), 7.54 (2H, m), 7.71 (2H, m), 7.91 (1H, s), 8.22 (1H, d, J=8.8Hz) 15

#### Reference Example 53

In 1,2-dimethoxyethane (10ml) and 6N hydrochloric acid (10ml) was dissolved methyl 7-[(4-ethylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate 20 (200mg), and the mixture was stirred at 100°C for 14 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-[(4-ethylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (135mg). 25

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.28 (3H, t, J=7.4Hz), 2.98 (2H, m), 3.06 (2H, q, J=7.4Hz), 3.75 (2H, m), 7.43 (2H, d, J=8.4Hz), 7.79 (2H, d, J=8.4Hz), 7.89-7.95 (2H, m), 8.06-8.12 (2H, m)

#### 30 Reference Example 54

In THF (35ml) was dissolved methyl 7-[(4-ethylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (870mg), and to the solution was added, under ice-cooling, 70% m-chloroperbenzoic acid (mCPBA) (1.11g). The mixture was stirred for 1 hour, and 35 to the mixture was added saturated sodium bicarbonate

solution. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate.

Under reduced pressure, the solvent was evaporated to give methyl 7-[(4-ethylsulfonyl)phenyl]-1,1-dioxo-2,3-

5 dihydro-1-benzothiepine-4-carboxylate (880mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.33 (3H, t, J=7.4Hz), 3.19 (2H, q, J=7.4Hz), 3.17 (2H, m), 3.67 (2H, m), 3.88 (3H, s), 7.72-7.83 (3H, m), 7.93 (1H, s), 8.02-8.07 (3H, m), 8.30 (1H, d, J=8.8Hz)

10 Reference Example 55

In 1,2-dimethoxyethane (35ml) and 6N hydrochloric acid (26ml) was dissolved methyl 7-[(4-ethylsulfonyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (870mg), and the solution was  
15 stirred at 100°C for 12 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-[(4-ethylsulfonyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (690mg).

20 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.15 (3H, t, J=7.4Hz), 3.00 (2H, m), 3.37 (2H, q, J=7.4Hz), 3.79 (2H, m), 7.92 (2H, s), 8.00-8.18 (5H, m), 8.25 (1H, s)

Reference Example 56

25 In DMF (96ml) was dissolved 4-bromobenzenethiol (12.0g), and to the solution was added at room temperature potassium carbonate (11.4g) and then added dropwise 1-iodopropane (6.6ml). The mixture was stirred for 2 hours and added to water, and the mixture was extracted with ethyl  
30 acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was (14.1g) dissolved in THF (126ml). To the solution was added dropwise at -78°C 1.6N n-butyllithium/hexane (42ml), and the mixture was stirred  
35 for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (19g) in THF (40ml), and the mixture

was stirred for 30 minutes and allowed to warm to room temperature. To the mixture was added 10% sulfuric acid (70ml), and the mixture was stirred for 15 minutes, extracted with ethyl acetate, washed with saturated brine and dried  
5 with magnesium sulfate. Under reduced pressure, the solvent was concentrated, and the residue washed with hexane/isopropylether to give 4-(propylthio)phenyl borate (6.0g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.08 (2H, t, J=7.0Hz), 1.60-1.82 (3H, m), 7.38 (2H, d, J=8.2Hz), 8.10 (2H, d, J=8.2Hz)

Reference Example 57

In toluene/ethanol/water (10/1/1.2ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (780mg), and to the solution were added 4-  
15 (propylthio)phenyl borate (743mg) and potassium carbonate (716mg). The mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (136mg), and the mixture was stirred at 90°C for 14 hours, cooled to room  
20 temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ ethyl acetate=2/1) to give methyl 1,1-dioxo-7-  
25 [(4-propylthio)phenyl]-2,3-dihydro-1-benzothiepine-4-carboxylate (798mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J=7.2Hz), 1.73 (2H, m), 2.97 (2H, t, J=7.2Hz), 3.15 (2H, m), 3.65 (2H, m), 3.87 (3H, s), 7.37-7.43 (2H, s), 7.49-7.55 (2H, m), 7.91 (1H, s), 8.21  
30 (1H, d, J=8.4Hz)

Reference Example 58

In 1,2-dimethoxyethane (23ml) and 6N hydrochloric acid (7.7ml) was dissolved methyl 1,1-dioxo-7-[(4-propylthio)phenyl]-2,3-dihydro-1-benzothiepine-4-  
35 carboxylate (770mg), and the mixture was stirred at 100°C for 16 hours, cooled to room temperature, extracted with

ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 1,1-dioxo-7-[(4-propylthio)phenyl]-2,3-dihydro-1-benzothiepine-4-carboxylic acid (700mg).

- 5 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.00 (3H, t, J=7.4Hz), 1.64 (2H, m), 2.99 (2H, m), 3.76 (2H, m), 7.43 (2H, d, J=8.6Hz), 7.89 (1H, s), 7.94 (1H, s), 8.10 (2H, m), 8.08 (2H, m)

Reference Example 59

- In DMF (96ml) was dissolved 4-bromobenzenethiol (12.0g), and to the solution was added at room temperature potassium carbonate (11.4g) and then added dropwise 1-iodobutane (13.9g). The mixture was stirred for 2 hours and added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue (14.3g) was dissolved in THF (130ml). To the solution was added dropwise at -78°C 1.6N n-butyllithium/hexane (40ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (18.1g) in THF (40ml), and the mixture was stirred for 30 minutes and allowed to warm to room temperature. To the mixture was added 10% sulfuric acid (70ml), and the mixture was stirred for 15 minutes, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was concentrated, and the residue washed with hexane/isopropylether to give 4-(butylthio)phenyl borate (6.1g).

- 30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.96 (3H, t, J=7.2Hz), 1.40-1.60 (2H, m), 1.67-1.79 (2H, m), 3.12 (2H, t, J=7.2Hz), 7.63 (2H, d, J=8.4Hz), 8.09 (2H, d, J=8.4Hz)

Reference Example 60

- In toluene/ethanol/water (10/1/1.2ml) was dissolved methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (730mg), and to the solution were added 4-(butylthio)phenyl borate (780mg) and potassium carbonate

(620mg). The mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (127mg), and the mixture was stirred at 90°C for 16 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ ethyl acetate=2/1) to give methyl 7-[(4-butylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (680mg).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.2Hz), 1.43-1.74 (2H, m), 2.99 (2H, t, J=7.4Hz), 3.15 (2H, m), 3.65 (2H, m), 3.87 (3H, s), 7.38-7.43 (2H, m), 7.52-7.55 (2H, m), 7.67-7.72 (2H, m), 7.91 (1H, s), 8.22 (1H, d, J=11.2Hz)

Reference Example 61

In 1,2-dimethoxyethane (20ml) and 6N hydrochloric acid (6.7ml) was dissolved methyl 7-[(4-butylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (670mg), and the mixture was stirred at 100°C for 16 hours, cooled to room temperature, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-[(4-butylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (620mg).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.90 (3H, t, J=7.2Hz), 1.14-1.65 (4H, m), 2.97 (2H, m), 3.04 (2H, t, J=7.2Hz), 3.76 (2H, m), 7.43 (2H, d, J=8.4Hz), 7.78 (2H, d, J=8.4Hz), 7.89-7.95 (2H, m), 8.10-8.14 (2H, m)

Reference Example 62

A solution of methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (700mg) in 1,2-dimethoxyethane (15ml) and 6N hydrochloric acid was refluxed for 18 hours and cooled to room temperature. The solvent was evaporated under reduced pressure to give colorless crystals, which were collected by filtration. The crystals



were washed with water, 2-propanol and diisopropylether to give colorless crystals of 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (634mg).

m.p. 290-300 °C

5 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.91-2.97 (2H, m), 3.73-3.80 (2H, m), 7.73 (1H, s), 7.84 (1H, dd, J=8.4, 2.0 Hz), 7.94 (1H, d, J=8.4 Hz), 8.08 (1H, d, J=2.0 Hz).

IR (KBr) 3088, 1680, 1419, 1286, 1165, 1133, 1097, 793, 744 cm<sup>-1</sup>

10 Anal. for C<sub>11</sub>H<sub>9</sub>O<sub>4</sub>SBr Calcd. C, 41.66 ; H, 2.86 ;  
Found. C, 41.82 ; H, 3.02.

Reference Example 63

To a suspension of 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (4.47g) in THF (90ml)  
15 were added at room temperature thionyl chloride (1.03ml) and DMF (1ml), and the mixture was stirred for 1 hour and added dropwise to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (3.41g) and triethylamine (7.9ml) in THF (30ml), at 0°C. The mixture  
20 was stirred for 3 hours and concentrated under reduced pressure, to which were added water. Precipitated colorless crystals were collected by filtration, and the crystals were washed with water, ethanol, 2-propanol and diisopropylether to give colorless crystals of 7-bromo-  
25 N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (4.94g).

m.p. 232-235 °C

30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.54-1.83 (4H, m), 2.21 (3H, s), 2.54-2.73 (1H, m), 3.11-3.18 (2H, m), 3.30-3.44 (2H, m), 3.58 (2H, s), 3.66-3.73 (2H, m), 3.99-4.10 (2H, m), 7.19 (1H, s), 7.33 (2H, d, J=8.3 Hz), 7.53 (2H, d, J=8.3 Hz), 7.62-7.71 (2H, m), 7.88 (1H, br s), 8.04 (1H, d, J=8.4 Hz).

IR (KBr) 3259, 1657, 1633, 1603, 1529, 1410, 1319, 1296,  
35 1132 cm<sup>-1</sup>

Anal. for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>SBr

Calcd. C, 55.49 ; H, 5.24 ; N, 5.39

Found. C, 55.56 ; H, 4.98 ; N, 5.22.

Reference Example 64

To a mixture of 4-bromo-2-chlorophenol (10.81g) and  
5 potassium carbonate (8.65g) in DMF (100ml) was added at room  
temperature ethyl iodide (4.17ml), and the mixture was  
stirred for 68 hours. To the mixture was added water, and  
the mixture was extracted with hexane. The organic layer  
was washed with saturated brine and dried with magnesium  
10 sulfate. Under reduced pressure, the solvent was  
evaporated to give pale yellow oil of 4-bromo-2-chloro-  
1-ethoxybenzene (12.28g).

To a solution of 4-bromo-2-chloro-1-ethoxybenzene  
(12.0g) in diethylether (100ml) was added dropwise at -  
15 78°C a solution of 1.6M n-butyllithium in hexane (35ml), and  
the mixture was stirred for 1 hour. To the mixture was added  
dropwise a solution of trimethyl borate (17ml) in  
diethylether (20ml), and the mixture was allowed to warm  
to room temperature and then stirred at room temperature  
20 for 2 hours. To the mixture was added dropwise 10% sulfuric  
acid (100ml), and the mixture was stirred for 1 hour and  
extracted with ethyl acetate. The organic layer was washed  
with saturated brine and dried with magnesium sulfate. The  
solvent was evaporated under reduced pressure to give  
25 colorless crystals, which were collected by filtration and  
washed with hexane to give colorless crystals of 3-  
chloro-4-ethoxyphenyl borate (4.44g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.53 (3H, t, J=7.0 Hz), 4.21 (2H,  
q, J=7.0 Hz), 7.02 (1H, d, J=8.2 Hz), 8.05 (1H, dd, J=8.2,  
30 1.8 Hz), 8.14 (1H, d, J=1.8 Hz).

Reference Example 65

To a mixture of 4-bromo-2-fluorophenol (10g) and  
potassium carbonate (8.7g) in DMF (100ml) was added at room  
temperature ethyl iodide (4.2ml), and the mixture was  
35 stirred for 68 hours. To the mixture was added water, and  
the mixture was extracted with hexane. The organic layer

was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give pale yellow oil of 4-bromo-1-ethoxy-3-fluorobenzene (11.46g).

- 5 To a solution of 4-bromo-1-ethoxy-3-fluorobenzene (11.10g) in diethylether (100ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (35ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (17ml) in  
10 diethylether (20ml), and the mixture was allowed to warm to room temperature and stirred at room temperature for 2 hours. To the mixture was added dropwise 10% sulfuric acid (100ml), and the mixture was stirred for 1 hour and extracted with ethyl acetate. The organic layer was washed with  
15 saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give colorless crystals, which were collected by filtration and washed with hexane to give colorless crystals of 4-ethoxy-3-fluorophenyl borate (4.66g).  
20 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.51 (3H, t, J=7.0 Hz), 4.20 (2H, q, J=7.0 Hz), 7.06 (1H, dd, J=8.0, 8.0 Hz), 7.82-7.93 (2H, m).

#### Reference Example 66

- To a solution of boron tribromide (25g) in  
25 dichloromethane (100ml) was added dropwise at 0°C a solution of 3,4-dimethoxybromobenzene (10.0g) in dichloromethane (20ml), and the mixture was stirred at room temperature for 15 hours and then added to ice/water to stop the reaction. The mixture was extracted with diethylether, and the  
30 organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give colorless crystals of 4-bromocathechol (8.43g).

- To a mixture of 4-bromocathechol (8.43g) and potassium carbonate (15.4g) in DMF (80ml) was added at room temperature  
35 ethyl iodide (7.5ml), and the mixture was stirred for 15 hours. To the mixture was added water, and the mixture was

extracted with hexane. The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue purified with silica gel column chromatography (ethyl acetate/hexane=1:4) to give yellow oil of 4-bromo-1,2-diethoxybenzene (10.06g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.44 (3H, t, J=7.0 Hz), 1.45 (3H, t, J=7.0 Hz), 4.06 (2H, q, J=7.0 Hz), 4.07 (2H, q, J=7.0 Hz), 6.74 (1H, d, J=8.8 Hz), 6.97-7.02 (2H, m).  
IR (neat) 1585, 1500, 1477, 1396, 1252, 1219, 1134, 1041, 845, 795 cm<sup>-1</sup>

#### Reference Example 67

To a mixture of 4-bromophenol (15g), sodium iodide (13.0g) and potassium carbonate (14.4g) in DMF (200ml) was added at room temperature 2-chloroethylmethyl ether (9ml), and the mixture was stirred at 80°C for 3 days. To the mixture was added water, and the mixture was extracted with diethylether. The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give orange oil of 1-bromo-4-(2-methoxyethoxy)benzene (17.44g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.45 (3H, s), 3.72-3.77 (2H, m), 4.06-4.11 (2H, m), 6.81 (2H, d, J=8.9 Hz), 7.37 (2H, d, J=8.9 Hz).  
IR (neat) 1587, 1489, 1454, 1284, 1246, 1128, 1061, 824 cm<sup>-1</sup>

#### Reference Example 68

To a mixture of 1,4-benzodioxane (5.0g) and sodium carbonate (5.9g) in hexane (100ml) was added dropwise at room temperature a solution of bromine (1.9ml) in hexane (20ml) for 1 hour and the mixture was stirred for 1 hour.

To the mixture was added an aqueous solution of sodium thiosulfate, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give orange oil of 6-bromo-2,3-dihydro-1,4-benzodioxine (7.48g).

Under argon atmosphere, to a solution of 6-bromo-2,3-dihydro-1,4-benzodioxine (7.48g) in THF (50ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (20ml), and the mixture was stirred for 1 hour.

- 5 To the mixture was added dropwise a solution of trimethyl borate (12ml) in THF (12ml), and the mixture was allowed to gradually warm to room temperature and then stirred at room temperature for 2 hours. To the mixture was added dropwise 10% sulfuric acid (100ml), and the mixture was
- 10 stirred for 30 minutes and extracted with ethyl acetate.

- The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. Precipitated colorless crystals were collected by filtration and washed with diisopropylether to give
- 15 colorless crystals of 2,3-dihydro-1,4-benzodioxin-6-yl borate (2.02g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 4.24-4.37 (4H, m), 6.97 (1H, d, J=8.4 Hz), 7.68-7.73 (2H, m).

#### Reference Example 69

- 20 To a mixture of 2,3-dihydrobenzofuran (11.06g) and sodium carbonate (14.8g) in hexane (100ml) was added dropwise at 0°C a solution of bromine (4.8ml) in hexane (20ml) for 1.5 hours, and the mixture was stirred at room temperature for 1 hour. To the mixture was added water, and
- 25 the mixture was extracted with hexane. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give gray crystals of 5-bromo-2,3-dihydrobenzofuran (17.64g).

- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.20 (2H, t, J=8.8 Hz), 4.57 (2H, t, J=8.8 Hz), 6.66 (1H, d, J=8.4 Hz), 7.17-7.30 (2H, m).
- 30

#### Reference Example 70

- To a mixture of 4-bromo-2-fluoroaniline (10.0g), potassium carbonate (21.8g) and sodium iodide (15.8g) in DMF (100ml) was added at room temperature bis(2-chloroethyl)
- 35 ether (7.53g), and the mixture was stirred at 90°C for 4 days.
- To the mixture was added bis(2-chloroethyl) ether (1ml).

and the mixture was stirred for 2 days. To the mixture was added water, and the mixture was extracted with ethyl acetate.

The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:5) to give orange oil (9.19g). The oil was dissolved in THF (100ml), and to the solution was added triethylamine (2.5ml). To the mixture was added at 0°C acetyl chloride (1.3ml), and the mixture was stirred for 1 hour. To the mixture was added water, and the mixture was extracted with ethyl acetate.

The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, the residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:4) to remove an acetyl compound and to give yellow oil of 4-(4-bromo-3-fluorophenyl)morpholine (6.89g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.03-3.08 (4H, m), 3.84-3.89 (4H, m), 6.76-6.85 (1H, m), 7.16-7.26 (2H, m).

IR (neat) 1565, 1497, 1450, 1257, 1236, 1209, 1119, 935, 866, 808 cm<sup>-1</sup>

#### Reference Example 71

Under argon atmosphere, a solution of 6-iodo-3,4-dihydro-2H-1-benzopyran (10.15g) in diethylether (80ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (27ml), and the mixture was stirred for 1 hour.

To the mixture was added dropwise a solution of trimethyl borate (14ml) in diethylether (14ml). The reaction mixture was allowed to gradually warm to room temperature, and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 1N hydrochloric acid (100ml), and the mixture was stirred for 1 hour and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. To the residue was added hexane and diisopropylether to give crystals, which were collected by

filtration and washed with hexane to give colorless crystals of 3,4-dihydro-2H-1-benzopyran-6-yl borate (2.00g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.97-2.15 (2H, m), 2.91 (2H, t, J=6.2 Hz), 4.27 (2H, t, J=5.1 Hz), 6.90 (1H, d, J=8.2 Hz), 7.90 (1H, d, J=1.4 Hz), 7.96 (1H, dd, J=8.2, 1.4 Hz).

Reference Example 72

To a solution of 7-bromo-3,4-dihydro-1-benzoxepin-5(2H)-one (20.0g) in trifluoroacetic acid (32ml) was added at room temperature triethylsilane (29.2ml), and the mixture was stirred for 2 hours and concentrated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was distilled under reduced pressure (0.8mmHg/123°C) to give colorless oil. The obtained oil (13.12g) was dissolved in ethanol (200ml), and to the solution was added platinum oxide (0.4g). The mixture was stirred under hydrogen atmosphere for 24 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified with silica gel column chromatography (hexane→ethyl acetate/hexane=1:19) to give colorless oil of 7-bromo-2,3,4,5-tetrahydro-1-benzoxepine (9.61g).

Under argon atmosphere, to a solution of 7-bromo-2,3,4,5-tetrahydro-1-benzoxepine (9.61g) in THF (50ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (29ml), and the mixture was stirred for 1 hour.

To the mixture was added dropwise a solution of trimethyl borate (14ml) in THF (14ml). The reaction mixture was allowed to gradually warm to room temperature and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 1N hydrochloric acid (100ml), and the mixture was stirred for 1 hour and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried with magnesium sulfate and

concentrated under reduced pressure. Precipitated colorless crystals were collected by filtration, which were washed with hexane to give colorless crystals of 2,3,4,5-tetrahydro-1-benzoxepin-7-yl borate (3.18g).

- 5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.72-1.88 (2H, m), 1.93-2.11 (2H, m), 2.91-3.04 (2H, m), 3.99-4.14 (2H, m), 7.10 (1H, d, J=7.8 Hz), 7.99-8.04 (2H, m).

#### Reference Example 73

- A solution of 5-bromo-2-hydroxyacetophenone 10.0g (46.5 milli mole), acetone (17ml) and pyrrolidine (3.9ml) in toluene (100ml) was refluxed for 4 hours. To the mixture was added acetone (17ml), and the mixture was refluxed for 15 hours. To the mixture was added 1N hydrochloric acid (100ml), and the mixture was extracted with ethyl acetate.
- 15 The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:7) to give yellow oil of 6-bromo-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one (7.57g).
- 20

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.46 (6H, s), 2.72 (2H, s), 6.83 (1H, d, J=8.8 Hz), 7.54 (1H, dd, J=8.8, 2.6 Hz), 7.97 (1H, d, J=2.6 Hz).

- IR (neat) 1689, 1597, 1464, 1414, 1373, 1319, 1282, 1225, 1167, 1132, 1066, 926, 827cm<sup>-1</sup>
- 25

#### Reference Example 74

- TO a solution of 6-bromo-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one (7.57g) in trifluoroacetic acid (21.4ml) was added at room temperature triethylsilane (10.4ml), and the mixture was stirred for 4 days. To the mixture was added triethylsilane (7.1ml), and the mixture was stirred at 50°C for 24 hours. To the mixture was added at 0°C 12N sodium hydroxide solution to make the solution alkaline, and the mixture was extracted with diethylether.
- 30
- 35 The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced



pressure. The residue was purified with silica gel column chromatography (hexane) to give colorless oil of 6-bromo-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (10.77g).

Under argon atmosphere, to a solution of 6-bromo-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran (10.77g) in THF (50ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (18ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise trimethyl borate (7.5ml) in THF (7.5ml). The reaction mixture was allowed to gradually warm to room temperature, and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 1N hydrochloric acid (100ml), and the mixture was stirred for 1 hour and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:4→1:2) to give colorless crystals of 2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-6-yl borate (170mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.38 (6H, s), 1.87 (2H, t, J=6.9 Hz), 2.90 (2H, t, J=6.9 Hz), 6.89 (1H, d, J=8.0 Hz), 7.94-7.98 (2H, m).

#### Reference Example 75

To a mixture of 4-bromo-2-fluorophenol (10.07g) and potassium carbonate (9.5g) in DMF (100ml) was added at room temperature 2-bromoethylethyl ether (6.0ml), and the mixture was stirred for 18 hours. To the mixture was added 2-bromoethylethyl ether (1.2ml), and the mixture was stirred at 55°C for 5 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water (thrice) and saturated brine (once), and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give pale yellow oil of 4-bromo-1-(2-ethoxyethoxy)-2-fluorobenzene (13.79g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=7.0 Hz), 3.60 (2H, q,

J=7.0 Hz), 3.78-3.83 (2H, m), 4.14-4.19 (2H, m), 6.84-6.92 (1H, m), 7.15-7.27 (2H, m).

IR (neat) 1502, 1306, 1269, 1207, 1130, 1055, 866  $\text{cm}^{-1}$

Reference Example 76

5 Under argon atmosphere, to a suspension of magnesium (1.34g) in THF (30ml) was added dropwise at room temperature a solution of 4-bromo-1-(2-ethoxyethoxy)-2-fluorobenzene (13.79g) and 1,2-dibromoethane (1ml) in THF (50ml) for 1 hour, and the mixture was stirred at 60°C for 1 hour. The  
10 reaction mixture was cooled to -78°C, to which was added dropwise a solution of trimethyl borate (17.6ml) in THF (20ml) for 30 minutes. The mixture was allowed to warm to room temperature and the mixture was stirred at room temperature for 2 hours. To the mixture was added 1N  
15 hydrochloric acid (100ml), and the mixture was stirred for 1 hour, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was washed with silica gel column chromatography (ethyl acetate/hexane = 1:1→2:1) to  
20 give colorless crystals of 4-(2-ethoxyethoxy)-3-fluorophenyl borate (1.40g).  
 $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.26 (3H, t, J=7.2 Hz), 3.64 (2H, q, J=7.2 Hz), 3.85-3.90 (2H, m), 4.26-4.31 (2H, m), 7.06-7.14 (1H, m), 7.82-7.94 (2H, m).

25 Reference Example 77

To a mixture of 3,4-dihydro-2H-1,5-benzodioxepine (8.86g) and sodium carbonate (9.4g) in hexane (100ml) was added dropwise at room temperature a solution of bromine (3.0ml) in hexane (30ml) for 2.5 hours, and the mixture was  
30 stirred for 24 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give orange oil. To the obtained oil (13.39g) in acetic acid  
35 (50ml) was added sodium acetate (4.1g), and then was added dropwise a solution of bromine (1.3ml) in acetic acid (25ml)

for 1 hour. The mixture was stirred for 24 hours and concentrated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate.

5 The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:4) to give orange oil of 7-bromo-3,4-dihydro-2H-1,5-benzodioxepine (13.17g).

10 To a solution of 7-bromo-3,4-dihydro-2H-1,5-benzodioxepine (13.17g) in THF (60ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (40ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (19ml) in THF  
15 (19ml) for 1 hour, and the mixture was stirred at -78°C for 1 hour. The reaction mixture was allowed to warm to room temperature and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 1N hydrochloric acid (100ml), and the mixture was stirred for  
20 1 hour and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to precipitate pale yellow crystals, which were collected by filtration and washed with hexane to give  
25 pale yellow crystals of 3,4-dihydro-2H-1,5-benzodioxepin-7-yl borate (2.99g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.17-2.31 (2H, m), 4.26-4.35 (4H, m), 7.06 (1H, d, J=7.8 Hz), 7.76-7.80 (2H, m).  
Reference Example 78

30 To a mixture of 4-bromo-2-chlorophenol (15.92g) and potassium carbonate (15.9g) in DMF (100ml) was added at room temperature 2-bromoethylethyl ether (9.51ml), and the mixture was stirred at 60°C for 18 hours. To the mixture was added water, and the mixture was extracted with  
35 diethylether. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was

evaporated under reduced pressure to give pale yellow oil of 4-bromo-2-chloro-1-(2-ethoxyethoxy)benzene (21.76g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=7.1 Hz), 3.63 (2H, q, J=7.1 Hz), 3.80-3.85 (2H, m), 4.13-4.18 (2H, m), 6.84 (1H, d, J=8.8 Hz), 7.31 (1H, dd, J=8.8, 2.6 Hz), 7.49 (1H, d, J=2.6 Hz).

IR (neat) 1481, 1290, 1263, 1250, 1124, 1056, 802 cm<sup>-1</sup>

#### Reference Example 79

To a solution of 4-bromo-2-chloro-1-(2-ethoxyethoxy)benzene (21.76g) in diethylether/THF (80/80ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (53ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution trimethyl borate (26ml) in THF (26ml) for 1 hour, and the mixture was stirred at -78°C for 1 hour. The reaction mixture was allowed to warm to room temperature, and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 1N hydrochloric acid (100ml), and the mixture was stirred for 1 hour and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to precipitate colorless crystals, which were collected by filtration and washed with diisopropyl ether to give colorless crystals of 3-chloro-4-(2-ethoxyethoxy)phenyl borate (10.24g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.27 (3H, t, J=7.0 Hz), 3.68 (2H, q, J=7.0 Hz), 3.88-3.93 (2H, m), 4.26-4.31 (2H, m), 7.06 (1H, d, J=8.4 Hz), 8.06 (1H, dd, J=8.4, 1.6 Hz), 8.15 (1H, d, J=1.6 Hz).

#### Reference Example 80

To a solution of 4-bromophenol (15.0g), tetrahydropyran-4-ol (9.0g) and triphenylphosphine (23.08g) in THF (100ml) was added dropwise at 0°C diethyl azodicarboxylate (40% toluene solution) (38.3g), and the mixture was stirred at room temperature for 3 days and concentrated under reduced pressure. To the residue was

added diethylether, and precipitated crystals were removed by filtration. The filtrate was concentrated, and the residue was dissolved in ethyl acetate. The solution was washed with 1N sodium hydroxide solution (X3) and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:4) to give colorless crystals of 4-(4-bromophenyloxy)tetrahydropyran (15.94g).

To a solution of 4-(4-bromophenyloxy)tetrahydropyran (15.73g) in THF (100ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (42ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (20ml) in THF (20ml) for 1 hour, and the mixture was stirred at -78°C for 1 hour.

The reaction mixture was allowed to warm to room temperature, and the mixture was stirred at room temperature for 2 hours.

To the mixture was added dropwise 1N hydrochloric acid (100ml), and the mixture was stirred for 1 hour and extracted

with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. The

solvent was evaporated under reduced pressure to give colorless crystals, which were collected by filtration and

washed with ethyl acetate/hexane to give colorless crystals of 4-(tetrahydropyran-4-yloxy)phenyl borate (4.30g). The

mother liquor was purified with silica gel column chromatography (ethyl acetate/hexane= 1:1) to give colorless crystals of 4-(tetrahydropyran-4-yloxy)phenyl borate (2.97g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.74-1.93 (2H, m), 1.98-2.15 (2H, m), 3.55-3.68 (2H, m), 3.95-4.08 (2H, m), 4.56-4.70 (1H, m), 7.02 (2H, d, J=8.6 Hz), 8.15 (2H, d, J=8.6 Hz).

#### Reference Example 81

To a solution of N-ethylaniline (10.0g) in DMF (50ml) was added dropwise at room temperature a solution of N-bromosuccinimide (14.69g) in DMF (100ml), and the mixture

was stirred at room temperature for 19 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give pale yellow oil of 4-bromo-N-ethylaniline (17.08g).

To a solution of 4-bromo-N-ethylaniline (17.08g) in DMF (100ml) were added at room temperature potassium carbonate (17.1g), sodium iodide (12.4g) and 2-bromoethylethyl ether (10.2ml), and the mixture was stirred at 90°C for 24 hours. To the mixture were added 2-bromoethylethyl ether (5.0ml), potassium carbonate (6.22g) and sodium iodide (6.64g), and the mixture was stirred for 2 days. To the mixture were added 2-bromoethylethyl ether (10.0ml), potassium carbonate (17.1g) and sodium iodide (12.4g), and the mixture was stirred at 90°C for 3 days. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:9) to give yellow oil of 4-bromo-N-(2-propoxyethyl)-N-ethylaniline (18.11g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.14 (3H, t, J=6.9 Hz), 1.20 (3H, t, J=7.0 Hz), 3.38 (2H, q, J=7.0 Hz), 3.41-3.59 (6H, m), 6.56 (2H, d, J=9.2 Hz), 7.26 (2H, d, J=9.2 Hz).  
IR (neat) 1591, 1498, 1394, 1373, 1352, 1267, 1192, 1115, 806cm<sup>-1</sup>

#### Reference Example 82

Under argon atmosphere, to a suspension of magnesium (1.57g) in THF (30ml) was added at room temperature a piece of iodine, and then was added dropwise at 40-50°C a solution of 4-bromo-N-(2-propoxyethyl)-N-ethylaniline (16.82g) in THF (50ml) for 1.5 hours. The mixture was stirred at 50°C for 2 hours, and the reaction mixture was cooled to -78°C, to which was added dropwise a solution of trimethyl borate

(20ml) in THF (20ml). The reaction mixture was allowed to warm to room temperature, and the mixture was stirred at room temperature for 18 hours. To the mixture was added 2N hydrochloric acid (100ml), and the mixture was stirred for 5 3 hours. To the mixture was added 8N sodium hydroxide solution to make the solution pH 7-8, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. To the residue was added hexane to give green 10 crystals, which were collected by filtration and washed with diisopropylether and hexane to give green crystals of 4-[N-(2-ethoxyethyl)-N-ethylamino]phenyl borate (1.21g). <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.09-1.28 (6H, m), 3.35-3.70 (8H, m), 6.76 (2H, d, J=8.8 Hz), 8.06 (2H, d, J=8.8 Hz).

15 Reference Example 83

To a solution of N-methylaniline (10.0g) in DMF (100ml) was added dropwise a solution of at room temperature N-bromosuccinimide (16.6g) in DMF (100ml), and the mixture was stirred at room temperature for 20 hours. The reaction 20 mixture was added to water, and the mixture was extracted with diethylether. The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give pale yellow oil of 4-bromo-N-methylaniline (18.18g).

25 To a solution of 4-bromo-N-methylaniline (18.18g) in DMF (150ml) were added at room temperature potassium carbonate (25.8g), sodium iodide (28.0g) and 2-bromoethylethyl ether (21ml), and the mixture was stirred at 90°C for 4 days. To the mixture were added 2- 30 bromoethylethyl ether (10.0ml), potassium carbonate (20.0g) and sodium iodide (13.3g), and the mixture was stirred for 2 days. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with 35 magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel

column chromatography (ethyl acetate/hexane=1:19) and distilled under reduced pressure (0.7mmHg, 131°C) to give yellow oil of 4-bromo-N-(2-ethoxyethyl)-N-methylaniline (17.63g).

- 5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.18 (3H, t, J=7.0 Hz), 2.95 (3H, s), 3.43-3.60 (6H, m), 6.59 (2H, d, J=9.2 Hz), 7.28 (2H, d, J=9.2 Hz).

IR (neat) 1593, 1497, 1373, 1350, 1115, 806 cm<sup>-1</sup>

Reference Example 84

- 10 Under argon atmosphere, to a suspension of magnesium (1.83g) in THF (30ml) was added at room temperature 1,2-dibromoethane (0.1ml). and then was added dropwise a solution of 4-bromo-N-(2-ethoxyethyl)-N-methylaniline (17.63g) in THF (30ml) for 1 hour. The mixture was stirred  
15 at 60°C for 2 hours and cooled to -78°C, to which was added dropwise a solution of trimethyl borate (23.0ml) in THF (23ml). The mixture was stirred at -78°C for 1 hour and allowed to warm to room temperature. To the mixture was added THF (50ml), and the mixture was stirred at room  
20 temperature for 1 hour. To the mixture was added at 0°C 3N hydrochloric acid (50ml), and the mixture was stirred at room temperature for 2.5 hours. To the mixture was added 2N sodium hydroxide solution to make the solution pH 7-8, and the mixture was extracted with ethyl acetate, washed  
25 with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. To the residue was added diisopropylether to give green crystals, which were collected by filtration and washed with diisopropylether to give green crystals of 4-[N-(2-ethoxyethyl)-N-methylamino]phenyl borate (8.51g).  
30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.21 (3H, t, J=7.0 Hz), 3.08 (3H, s), 3.51 (2H, q, J=7.0 Hz), 3.59-3.68 (4H, m), 6.79 (2H, d, J=8.8 Hz), 8.08 (2H, d, J=8.8 Hz).

Reference Example 85

- 35 To a solution of 2-(N-ethylanilino)ethanol (17.83g) in DMF (300ml) was added at 0°C sodium hydride (60%, 4.74g),



and the mixture was stirred at 0°C for 30 minutes and at room temperature for 30 minutes. To the mixture was added propyl iodide (11.0ml), and the mixture was stirred at 50°C for 19 hours. To the mixture was added water, and the mixture was  
5 extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:19) to give colorless oil of N-ethyl-  
10 N-(2-propoxyethyl)aniline (10.18g).

To a solution of N-ethyl-N-(2-propoxyethyl)aniline (10.18g) in DMF (50ml) was added at room temperature a solution of N-bromosuccinimide (7.45g) in DMF (50ml) for 40 minutes, and the mixture was stirred for 3 hours. To the  
15 mixture was added a solution of N-bromosuccinimide (0.2g) in DMF (10ml), and the mixture was stirred for 15 hours.

The reaction mixture was added to water, and the mixture was extracted with diethylether. The organic layer was washed with water (twice) and saturated brine, and dried  
20 with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was distilled under reduced pressure (0.7mmHg, 134°C) to give pale yellow oil of 4-bromo-N-ethyl-N-(2-propoxyethyl)aniline (9.49g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.91 (3H, t, J=7.4 Hz), 1.14 (3H, t, J=7.1 Hz), 1.50-1.67 (2H, m), 3.31-3.60 (8H, m), 6.56 (2H, d, J=9.2 Hz), 7.26 (2H, d, J=9.2 Hz).

IR (neat) 1591, 1498, 1356, 1267, 1192, 1113, 804 cm<sup>-1</sup>

#### Reference Example 86

Under argon atmosphere, to a suspension of magnesium  
30 (0.89g) in THF (30ml) was added at room temperature 1,2-dibromoethane (0.1ml) and then was added at 60°C a solution of 4-bromo-N-ethyl-N-(2-propoxyethyl)aniline (9.49g) in THF (40ml) for 40 minutes. The mixture was stirred for 2 hours and cooled to -78°C. To the mixture was  
35 added a solution of trimethyl borate (11ml) in THF (11ml) for 1 hour, and the mixture was stirred at -78°C for 1 hour.

The reaction mixture was allowed to warm to room temperature, and the mixture was stirred at room temperature for 2 hours.

To the mixture was added 3N hydrochloric acid (25ml), and the mixture was stirred for 2 hours. To the mixture was added  
5 2N sodium hydroxide solution to make the solution pH 7-8, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and washed with hexane to give  
10 green crystals of 4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl borate (0.7g). The mother liquor was purified with silica gel column chromatography (ethyl acetate/hexane=1:1) to give green crystals of 4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl borate (2.1g).  
15 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ: 0.93 (3H, t, J=7.5 Hz), 1.21 (3H, t, J=7.0 Hz), 1.53-1.69 (2H, m), 3.39-3.62 (8H, m), 6.76 (2H, d, J=9.0 Hz), 8.06 (2H, d, J=8.0 Hz).

Reference Example 87

To a solution of N-methylaniline (10.0g) in DMF (100ml)  
20 was added dropwise at room temperature a solution of N-bromosuccinimide (16.6g) in DMF (100ml), and the mixture was stirred for at room temperature for 20 hours. The reaction mixture was added to water, and the mixture was extracted with diethylether. The organic layer was washed  
25 with water (thrice) and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give yellow oil of 4-bromomethylaniline (17.93g).

To a solution of 4-bromomethylaniline (17.93g) in DMF (300ml) were added at room temperature potassium carbonate  
30 (52g), sodium iodide (42g) and 2-bromoethylethyl ether (35ml), and the mixture was stirred at 90°C for 4 days. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water (thrice) and saturated brine, and dried with magnesium  
35 sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel

column chromatography (ethyl acetate/hexane=1:19) and distilled under reduced pressure (0.5mmHg, 124-127°C) to give yellow oil of 4-bromo-N-methyl-N-(2-propoxyethyl)aniline (17.95g).

- 5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.90 (3H, t, J=7.3 Hz), 1.46-1.65 (2H, m), 2.95 (3H, s), 3.37 (2H, t, J=6.6 Hz), 3.45-3.59 (4H, m), 6.58 (2H, d, J=9.2 Hz), 7.28 (2H, d, J=9.2 Hz).  
IR (neat) 1593, 1502, 1373, 1352, 1117, 806cm<sup>-1</sup>

Reference Example 88

- 10 Under argon atmosphere, to a suspension of magnesium (1.76g) in THF (30ml) was added at room temperature 1,2-dibromoethane (0.1ml) and then was added a solution of 4-bromo-N-methyl-N-(2-propoxyethyl)aniline (17.95g) in THF (30ml) for 30 minutes. The mixture was stirred at 60°C  
15 for 1.5 hours and cooled to -78°C, to which was added a solution of trimethyl borate (22ml) in THF (22ml) for 30 minutes. The mixture was stirred at -78°C for 1 hour, allowed to warm to room temperature and stirred for 2 hours.  
To the mixture was added 3N hydrochloric acid (50ml), and  
20 the mixture was stirred for 30 minutes. To the mixture was added 2N sodium hydroxide solution to make the solution pH 7-8, and the mixture was extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which  
25 were collected by filtration and washed with hexane to give green crystals of 4-[N-methyl-N-(2-propoxyethyl)amino]phenyl borate (5.18g).

- 30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.5 Hz), 1.49-1.68 (2H, m), 3.08 (3H, s), 3.41 (2H, t, J=6.7 Hz), 3.55-3.67 (4H, m), 6.78 (2H, d, J=8.7 Hz), 8.08 (2H, d, J=8.7 Hz).

Reference Example 89

- To a solution of 4-bromo-2-ethoxyphenol (8.0g) in DMF (50ml) were added at room temperature potassium carbonate (7.65g), sodium iodide (6.64g) and 2-chloroethylpropylether (5.6ml), and the mixture was stirred  
35 at 90°C for 24 hours. To the mixture was added water, and

the mixture was extracted with ethyl acetate. The organic layer was washed with water, 1N sodium hydroxide solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was  
5 purified with silica gel column chromatography (ethyl acetate/hexane=1:4) to give yellow oil of 4-bromo-2-ethoxy-1-(2-propoxyethoxy)benzene (10.33g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.5 Hz), 1.43 (3H, t, J=7.0 Hz), 1.53-1.72 (2H, m), 3.50 (2H, t, J=6.8 Hz), 3.79  
10 (2H, t, J=4.9 Hz), 4.05 (2H, q, J=7.0 Hz), 4.14 (2H, t, J=4.9 Hz), 6.80 (1H, d, J=9.2 Hz), 6.98-7.02 (2H, m).  
IR (neat) 1587, 1498, 1475, 1454, 1402, 1294, 1254, 1219, 1137, 1041, 934 cm<sup>-1</sup>

## Reference Example 90

15 Under argon atmosphere, to a solution of 4-bromo-2-ethoxy-1-(2-propoxyethoxy)benzene (10.25g) in THF/diethylether (30/30ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (23ml), and the mixture was stirred at -78°C for 1 hour. To the mixture was  
20 added a solution of trimethyl borate (98.1milli mole) in THF (11ml) for 1 hour, and the mixture was stirred at -78°C for 1 hour and allowed to warm to room temperature. The mixture was stirred at room temperature for 2 hours. To the mixture was added 1N hydrochloric acid (100ml), and the  
25 mixture was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and washed with hexane to give colorless crystals  
30 of 3-ethoxy-4-(2-propoxyethoxy)phenyl borate (3.09g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.5 Hz), 1.50 (3H, t, J=6.9 Hz), 1.57-1.72 (2H, m), 3.55 (2H, t, J=6.8 Hz), 3.84-3.90 (2H, m), 4.17-4.29 (4H, m), 7.04 (1H, d, J=8.0 Hz), 7.70 (1H, d, J=1.4 Hz), 7.81 (1H, dd, J=8.0, 1.4 Hz).

## 35 Reference Example 91

To a solution of 4-bromo-2-chlorophenol (10g) in DMF

(200ml) were added at room temperature potassium carbonate (9.99g), sodium iodide (7.95g) and 2-chloroethylpropylether (6.7ml), and the mixture was stirred at 90°C for 24 hours. To the mixture was added water, and the mixture was extracted with hexane. The organic layer was washed with water, 1N sodium hydroxide solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give pale yellow oil of 4-bromo-2-chloro-1-(2-propoxyethoxy)benzene (14.91g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.3 Hz), 1.54-1.70 (2H, m), 3.52 (2H, t, J=6.6 Hz), 3.82 (2H, t, J=4.9 Hz), 4.16 (2H, t, J=4.9 Hz), 6.85 (1H, d, J=8.8 Hz), 7.31 (1H, dd, J=8.8, 2.4 Hz), 7.50 (1H, d, J=2.4 Hz).  
IR (neat) 1584, 1483, 1452, 1290, 1265, 1250, 1128, 1086, 1066, 800cm<sup>-1</sup>

#### Reference Example 92

Under argon atmosphere, to a solution of 4-bromo-2-chloro-1-(2-propoxyethoxy)benzene (14.91g) in THF/diethylether (40/40ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (33ml), and the mixture was stirred at -78°C for 1 hour. To the mixture was added a solution of trimethyl borate (16.1ml) in THF (16ml) for 1 hour, and the mixture was stirred at -78°C for 1 hour. The reaction mixture was allowed to warm to room temperature and then stirred at room temperature for 36 hours. To the mixture was added 1N hydrochloric acid (100ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:1→2:1) to give colorless crystals of 3-chloro-4-(2-propoxyethoxy)phenyl borate (3.31g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.96 (3H, t, J=7.3 Hz), 1.56-1.70 (2H, m), 3.57 (2H, t, J=6.6 Hz), 3.89 (2H, t, J=5.0 Hz), 4.28 (2H, t, J=5.0 Hz), 7.06 (1H, d, J=8.2 Hz), 8.05 (1H, dd, J=8.2, 1.4 Hz), 8.14 (1H, d, J=1.4 Hz).

## Reference Example 93

To a solution of 4-bromo-2-methylphenol (10.46g) in DMF (100ml) were added at room temperature potassium carbonate (11.5g), sodium iodide (9.97g) and 2-chloroethylpropylether (5.6ml), and the mixture was stirred at 90°C for 7 days. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, 1N sodium hydroxide solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane=1:9) to give pale yellow oil of 4-bromo-2-methyl-1-(2-propoxyethoxy)benzene (11.7g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J=7.6 Hz), 1.52-1.71 (2H, m), 2.20 (3H, s), 3.50 (2H, t, J=6.8 Hz), 3.79 (2H, t, J=5.0 Hz), 4.09 (2H, t, J=5.0 Hz), 6.69 (1H, d, J=9.2 Hz), 7.18-7.27 (2H, m).

IR (neat) 1491, 1454, 1296, 1248, 1190, 1132 cm<sup>-1</sup>

## Reference Example 94

Under argon atmosphere, to a suspension of magnesium (1.14g) in THF (10ml) was added at room temperature 1,2-dibromoethane (0.05ml), and then was added dropwise a solution of 4-bromo-2-methyl-1-(2-propoxyethoxy)benzene (11.7g) in THF (50ml) for 20 minutes. The mixture was stirred at 60°C for 1.5 hours. The reaction mixture was cooled to -78°C, and to the mixture was added dropwise trimethyl borate (10.0ml) in THF (10ml). The mixture was stirred at -78°C for 1 hour and allowed to warm to room temperature. To the mixture was added THF (50ml), and the mixture was stirred at room temperature for 2 hours. To the mixture was added 1N hydrochloric acid (100ml), and the mixture was stirred for 30 minutes, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. To the residue was added diisopropylether, and precipitated green crystals were collected by filtration, which were washed

with hexane to give colorless crystals of 3-methyl-4-(2-propoxyethoxy)phenyl borate (5.44g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.96 (3H, t, J=7.5 Hz), 1.56-1.75 (2H, m), 2.34 (3H, s), 3.55 (2H, t, J=6.6 Hz), 3.86 (2H, t, J=5.0),  
5 4.22 (2H, t, J=5.0), 6.94 (1H, d, J=8.1 Hz), 7.97 (1H, s), 8.05 (1H, d, J=8.1 Hz).

Working Example 49 (Production of Compound 48)

Under argon atmosphere, a mixture of 7-bromo-N-[4-  
10 [[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300m), 2,4-dimethoxyphenyl borate (116mg) and potassium carbonate (160mg) in toluene/ethanol/water (6/0.6/0.6ml) was stirred at room temperature for 1 hour. To the mixture was added  
15 tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 7 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

The residue was purified with silica gel column  
20 chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-(2,4-dimethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
25 (Compound 48) (216mg).

m.p. 175-178 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.54-1.82 (4H, m), 2.20 (3H, s), 2.55-2.74 (1H, m), 3.16 (2H, t, J=6.7 Hz), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.72 (2H, t, J=6.7 Hz), 3.82 (3H, s), 3.87  
30 (3H, s), 3.99-4.10 (2H, m), 6.57-6.62 (2H, m), 7.23-7.34 (4H, m), 7.54 (2H, d, J=8.4 Hz), 7.62-7.66 (2H, m), 7.97 (1H, br s), 8.16 (1H, d, J=8.2 Hz).

IR (KBr) 3284, 1649, 1610, 1518, 1313, 1296, 1211, 1130 cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S · 0.2H<sub>2</sub>O Calcd. C, 66.23 ; H, 6.32 ; N,  
35 4.83 ; Found. C, 65.93 ; H, 6.33 ; N, 4.79.

Working Example 50 (Production of Compound 49)

- Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 3-chloro-4-  
ethoxyphenyl borate (127mg) and potassium carbonate (160mg)  
in toluene/ethanol/water (10/1/1ml) was stirred at room  
temperature for 1 hour. To the mixture was added  
tetrakis(triphenylphosphine)palladium (33mg), and the  
mixture was refluxed for 30 hours, cooled, extracted with  
ethyl acetate, washed with saturated brine, dried with  
magnesium sulfate and concentrated under reduced pressure.  
The residue was purified with silica gel column  
chromatography (ethanol/ethyl acetate=1:4) to give  
crystals, which were recrystallized from ethanol to give  
colorless crystals of 7-(3-chloro-4-ethoxyphenyl)-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (Compound 49) (38mg).  
m.p. 201-204 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.52 (3H, t, J=7.0 Hz), 1.63-1.85 (4H, m), 2.21 (3H, s), 2.56-2.74 (1H, m), 3.14-3.20 (2H, m), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.70-3.76 (2H, m), 3.99-4.10 (2H, m), 4.18 (2H, q, J=7.0 Hz), 7.02 (1H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.46 (1H, dd, J=8.8, 2.2 Hz), 7.55 (2H, d, J=8.8 Hz), 7.61-7.68 (3H, m), 7.91 (1H, br s), 8.21 (1H, d, J=8.0 Hz).
- IR (KBr) 3332, 1649, 1599, 1516, 1311, 1294, 1269, 1165, 1130, 820 cm<sup>-1</sup>
- Anal. for C<sub>32</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub>SCl
- Calcd. C, 64.58 ; H, 5.93 ; N, 4.71  
Found. C, 64.53 ; H, 5.81 ; N, 4.70.
- Working Example 51 (Production of Compound 50)
- Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 4-ethoxy-3-



fluorophenyl borate (117mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 24 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:4) to give crystals, which were recrystallized from ethanol to give pale yellow crystals of 7-(4-ethoxy-3-fluorophenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 50) (137mg).

m.p. 233-235 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.50 (3H, t, J=6.9 Hz), 1.64-1.84 (4H, m), 2.21 (3H, s), 2.56-2.72 (1H, m), 3.14-3.20 (2H, m), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.70-3.76 (2H, m), 3.98-4.11 (2H, m), 4.18 (2H, q, J=6.9 Hz), 7.02-7.11 (1H, m), 7.30-7.40 (5H, m), 7.55 (2H, d, J=8.4 Hz), 7.60 (1H, d, J=1.8 Hz), 7.66 (1H, dd, J=8.2, 1.8 Hz), 7.92 (1H, br s), 8.21 (1H, d, J=8.2 Hz).

IR (KBr) 3432, 1659, 1603, 1522, 1309, 1130 cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>35</sub>N<sub>2</sub>O<sub>5</sub>SF

Calcd. C, 66.42 ; H, 6.10 ; N, 4.84

Found. C, 66.16 ; H, 6.09 ; N, 4.83.

Working Example 52 (Production of Compound 51)

To a solution of 4-bromo-1,2-diethoxybenzene (9.74g) in THF (80ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (27ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (14ml) in THF (14ml). The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 2 hours. To the mixture was added dropwise 10% sulfuric acid (100ml), and the mixture was stirred for 30 minutes and extracted with ethyl acetate.

The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give colorless crystals, which were collected by filtration and washed with hexane to give colorless crystals of 3,4-diethoxyphenyl borate (5.22g).

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3,4-diethoxyphenyl borate (134mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 7 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were recrystallized from ethanol to give pale yellow crystals of 7-(3,4-diethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 51) (214mg). m.p. 224-226 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.49 (6H, t, J=7.0 Hz), 1.66-1.83 (4H, m), 2.21 (3H, s), 2.57-2.72 (1H, m), 3.17 (2H, t, J=6.8 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.72 (2H, t, J=6.8 Hz), 3.98-4.11 (2H, m), 4.16 (2H, q, J=7.0 Hz), 4.18 (2H, q, J=7.0 Hz), 6.97 (1H, d, J=8.0 Hz), 7.11-7.16 (2H, m), 7.31-7.35 (3H, m), 7.56 (2H, d, J=8.4 Hz), 7.60-7.68 (2H, m), 7.96 (1H, s), 8.18 (1H, d, J=8.4 Hz).

IR (KBr) 3329, 1653, 1599, 1518, 1315, 1250, 1134, 810 cm<sup>-1</sup>  
Anal. for C<sub>34</sub>H<sub>46</sub>N<sub>2</sub>O<sub>6</sub>S · 0.2H<sub>2</sub>O

Calcd. C, 67.13 ; H, 6.69 ; N, 4.60

Found. C, 67.01 ; H, 6.55 ; N, 4.48.

Working Example 53 (Production of Compound 52)

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-

yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3,4-dimethoxyphenyl borate (116mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (40mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-(3,4-dimethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 52) (112mg).  
m.p. 195-197 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.67-1.84 (4H, m), 2.21 (3H, s), 2.56-2.74 (1H, m), 3.14-3.21 (2H, m), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 3.95 (3H, s), 3.97 (3H, s), 3.99-4.11 (2H, m), 6.98 (1H, d, J=8.2 Hz), 7.10 (1H, d, J=2.0 Hz), 7.18 (1H, dd, J=8.2, 2.0 Hz), 7.33 (2H, d, J=8.4 Hz), 7.37 (1H, s), 7.55 (2H, d, J=8.4 Hz), 7.62 (1H, d, J=2.0 Hz), 7.68 (1H, dd, J=8.4, 2.0 Hz), 7.95 (1H, s), 8.20 (1H, d, J=8.4 Hz).  
IR (KBr) 3327, 1668, 1595, 1520, 1311, 1257, 1136 cm<sup>-1</sup>  
Anal. for C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S · 0.2H<sub>2</sub>O  
Calcd. C, 66.23 ; H, 6.32 ; N, 4.82  
Found. C, 66.19 ; H, 6.52 ; N, 4.73.  
Working Example 54 (Production of Compound 53)

To a solution of 1-bromo-4-(2-methoxyethoxy)benzene (17.0g) in diethylether/THF (150/50ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (50ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (24.8ml) in THF (25ml). The reaction mixture was allowed to warm to room temperature and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 10% sulfuric

acid (100ml), and the mixture was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate.

The solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane= 1:1) to give colorless crystals of 4-(2-methoxyethoxy)phenyl borate (7.17g).

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 4-(2-methoxyethoxy)phenyl borate (124mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenyl)phosphinepalladium (40mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-[4-(2-methoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 53) (246mg).

m.p. 227-231 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.64-1.84 (4H, m), 2.21 (3H, s), 2.55-2.74 (1H, m), 3.13-3.19 (2H, m), 3.32-3.44 (2H, m), 3.47 (3H, s), 3.58 (2H, s), 3.69-3.81 (4H, m), 3.99-4.09 (2H, m), 4.16-4.21 (2H, m), 7.04 (2H, d, J=8.8 Hz), 7.30-7.35 (3H, m), 7.52-7.56 (4H, m), 7.62-7.69 (2H, m), 7.92 (1H, s), 8.19 (1H, d, J=8.4 Hz).

IR (KBr) 3246, 1655, 1605, 1518, 1410, 1315, 1294, 1254, 1167, 1128, 825 cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 67.10 ; H, 6.48 ; N, 4.74

Found. C, 66.85 ; H, 6.40 ; N, 4.62.

## Working Example 55 (Production of Compound 54)

To a solution of 4-bromo-N,N-diethylaniline (17.0g) in THF (150ml) was added dropwise at -78°C a solution of 1.6M n-butyllithium in hexane (51ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (25ml) in THF (25ml). The reaction mixture was allowed to warm to room temperature, and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 1N hydrochloric acid (200ml), and the mixture was stirred for 1 hour. To the mixture was added saturated sodium bicarbonate solution to make the solution pH 7, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give colorless crystals, which were collected by filtration. The crystals were washed with diisopropylether to give colorless crystals of 4-diethylaminophenyl borate (2.47g). The mother liquor was concentrated to give gray crystals, which were collected by filtration and washed with hexane to give 4-diethylaminophenyl borate (4.00g).

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 4-diethylaminophenyl borate (123mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 7 hours, cooled, extracted with ethyl acetate/THF (1:1), washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were recrystallized from ethanol to give yellow crystals of 7-(4-diethylaminophenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-

benzothiepine-4-carboxamide (Compound 54) (198mg).

m.p. 240-246 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.21 (6H, t, J=6.9 Hz), 1.65-1.82 (4H, m), 2.21 (3H, s), 2.56-2.75 (1H, m), 3.15 (2H, t, J=7.0 Hz),  
5 3.31-3.50 (6H, m), 3.58 (2H, s), 3.68-3.74 (2H, m), 3.98-4.08 (2H, m), 6.75 (2H, d, J=9.2 Hz), 7.31-7.35 (3H, m), 7.49-7.67 (6H, m), 7.93 (1H, br s), 8.14 (1H, d, J=8.2 Hz).

IR (KBr) 3292, 1657, 1606, 1527, 1408, 1315, 1296, 1271, 1128, 812 cm<sup>-1</sup>

10 Anal. for C<sub>34</sub>H<sub>41</sub>N<sub>3</sub>O<sub>4</sub>S · 0.5H<sub>2</sub>O

Calcd. C, 68.42 ; H, 7.09 ; N, 7.04

Found. C, 68.39 ; H, 7.11 ; N, 7.02.

Working Example 56 (Production of Compound 55)

Under argon atmosphere, a mixture of 7-bromo-N-  
15 [4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 2,3-dihydro-1,4-benzodioxin-6-yl borate (114mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at  
20 room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.  
25 The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:2) to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-(2,3-dihydro-1,4-benzodioxin-6-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 55) (257mg).

m.p. 248-251 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.66-1.84 (4H, m), 2.21 (3H, s), 2.57-2.74 (1H, m), 3.17 (2H, t, J=6.9 Hz), 3.31-3.43 (2H, m), 3.58 (2H, s), 3.73 (2H, t, J=6.9 Hz), 3.99-4.10 (2H, m), 4.32 (4H, s), 6.98 (1H, d, J=8.6 Hz), 7.08-7.13 (2H,

m), 7.31-7.35 (3H, m), 7.55 (2H, d, J=8.4 Hz), 7.61-7.68 (2H, m), 7.90 (1H, s), 8.19 (1H, d, J=-8.4 Hz).

IR (KBr) 3246, 1653, 1599, 1514, 1410, 1317, 1290, 1246, 1128, 1068, 816  $\text{cm}^{-1}$

5 Anal. for  $\text{C}_{32}\text{H}_{34}\text{N}_2\text{O}_6\text{S}$

Calcd. C, 66.88 ; H, 5.96 ; N, 4.87

Found. C, 66.70 ; H, 6.15 ; N, 4.74.

Working Example 57 (Production of Compound 56)

Under argon atmosphere, to a solution of 5-bromo-  
10 2,3-dihydrobenzofuran (17.64g) in THF (150ml) was added dropwise at  $-78^\circ\text{C}$  a solution of 1.6M n-butyllithium in hexane (60ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (30ml) in THF (30ml). The reaction mixture was allowed to  
15 gradually warm to room temperature, and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise 10% sulfuric acid (100ml), and the mixture was stirred for 30 minutes and extracted with ethyl acetate.

The organic layer was washed with water and saturated brine,  
20 dried with magnesium sulfate and concentrated under reduced pressure to give colorless crystals, which were collected by filtration. The crystals were washed with diisopropylether to give colorless crystals of 2,3-dihydrobenzofuran-5-yl borate (8.28g).

25 Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 2,3-dihydrobenzofuran-5-yl borate (104mg) and potassium  
30 carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with  
35 magnesium sulfate and concentrated under reduced pressure.

The residue was purified with silica gel column

- chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give pale yellow crystals of 7-(2,3-dihydrobenzofuran-5-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 56) (246mg).  
m.p. 214-216 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.57-1.84 (4H, m), 2.21 (3H, s), 2.54-2.76 (1H, m), 3.13-3.20 (2H, m), 3.29 (2H, t, J=8.6 Hz), 3.13-3.44 (2H, m), 3.58 (2H, s), 3.69-3.76 (2H, m), 4.00-4.09 (2H, m), 4.66 (2H, t, J=8.6 Hz), 6.89 (1H, d, J=8.4 Hz), 7.31-7.40 (4H, m), 7.45 (1H, s), 7.55 (2H, d, J=8.4 Hz), 7.60 (1H, d, J=1.6 Hz), 7.65 (1H, dd, J=8.4, 1.6 Hz), 7.94 (1H, s), 8.18 (1H, d, J=8.4 Hz).
- IR (KBr) 3265, 1653, 1632, 1597, 1527, 1410, 1317, 1294, 1234, 1128, 818 cm<sup>-1</sup>  
Anal. for C<sub>32</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>S · 0.2H<sub>2</sub>O  
Calcd. C, 68.35 ; H, 6.17 ; N, 4.98  
Found. C, 68.24 ; H, 6.21 ; N, 4.80.
- Working Example 58 (Production of Compound 57)  
Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (500mg), 4-methoxycarbonylphenyl borate (191mg) and potassium carbonate (266mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (56mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:2→1:1) to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-(4-methoxycarbonylphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-



yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (290mg).

m.p. 269-273 °C (dec.)

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.66-1.83 (4H, m), 2.21 (3H, s),  
5 2.56-2.72 (1H, m), 3.15-3.22 (2H, m), 3.31-3.44 (2H, m),  
3.57 (2H, s), 3.70-3.77 (2H, m), 3.96 (3H, s), 3.98-4.10  
(2H, m), 7.32 (2H, d, J=8.4 Hz), 7.37 (1H, s), 7.54 (2H,  
d, J=8.4 Hz), 7.64-7.68 (3H, m), 7.74 (1H, dd, J=8.0, 2.0  
Hz), 7.95 (1H, s), 8.16 (2H, d, J=8.4 Hz), 8.26 (1H, d, J=8.0  
10 Hz).

IR (KBr) 3280, 1722, 1657, 1603, 1524, 1410, 1317, 1290,  
1130, 1109, 816 cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 66.88 ; H, 5.96 ; N, 4.87

15 Found. C, 66.65 ; H, 5.83 ; N, 5.03.

Working Example 59 (Production of Compound 58)

To a solution of 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-  
1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
20 (2.5g) in THF (200ml) was added at room temperature methane  
sulfonic acid (0.29ml), and the mixture was stirred for 0.5  
hours. To the mixture was added 2-propanol, and the mixture  
was concentrated under reduced pressure. Precipitated  
crystals were dissolved at 90°C in 2-propanol, and the  
25 mixture was cooled to room temperature and then cooled to  
0°C to give crystals, which were collected by filtration and  
washed with diethylether to give colorless crystals of  
7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-  
4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
30 benzothiepine-4-carboxamide · methane sulfonate (Compound  
58) (2.56g).

m.p. 161-166 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45 (3H, t, J=7.0 Hz), 1.76-2.16 (4H,  
m), 2.56-2.65 (3H, m), 2.78 (3H, s), 3.04-3.14 (2H, m),  
35 3.20-3.52 (3H, m), 3.72-3.85 (2H, m), 3.90-4.05 (3H, m),  
4.09 (2H, q, J=7.0 Hz), 4.21-4.33 (1H, m), 7.00 (2H, d, J=8.8

Hz), 7.46 (2H, d, J=8.8 Hz), 7.59-7.68 (3H, m), 7.78-7.88 (4H, m), 8.15 (1H, d, J=8.4 Hz), 9.33 (1H, s).

IR (KBr) 3427, 1664, 1605, 1520, 1294, 1248, 1217, 1165, 1126, 1039, 825  $\text{cm}^{-1}$

5 Anal. for  $\text{C}_{33}\text{H}_{40}\text{N}_2\text{O}_8\text{S}_2 \cdot 0.5\text{H}_2\text{O}$

Calcd. C, 59.53 ; H, 6.21 ; N, 4.21

Found. C, 59.28 ; H, 6.04 ; N, 4.39.

Working Example 60 (Production of Compound 59)

To a solution of 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (500mg) in THF (37.5ml) was added at room temperature citric acid (171.1mg), and the mixture was stirred for 1 hour and concentrated under reduced pressure. To the residue was added ethanol to give crystals, which were collected by filtration and recrystallized from water/ethanol=1:10 to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  $\cdot$  1/2 citrate (Compound 59) (413mg).

m.p. 241-245  $^{\circ}\text{C}$  (dec.)

$^1\text{H}$ -NMR (200MHz, DMSO- $d_6$ )  $\delta$  1.36 (3H, t, J=7.0 Hz), 1.50-1.73 (2H, m), 1.76-1.90 (2H, m), 2.30 (3H, s), 2.58 (1H, s), 2.61 (1H, s), 2.82-3.03 (1H, m), 3.05-3.11 (2H, m), 3.22-3.51 (2H, m), 3.73-3.87 (4H, m), 3.89-4.01 (2H, m), 4.10 (2H, q, J=7.0 Hz), 7.08 (2H, d, J=8.8 Hz), 7.36 (2H, d, J=8.8 Hz), 7.54 (1H, s), 7.74 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), 7.87 (1H, dd, J=8.2, 1.8 Hz), 8.04-8.09 (2H, m), 10.26 (1H, s).

30 IR (KBr) 3336, 1726, 1664, 1603, 1522, 1317, 1292, 1248, 1168, 1128, 827  $\text{cm}^{-1}$

Anal. for  $\text{C}_{35}\text{H}_{40}\text{N}_2\text{O}_{8.5}\text{S} \cdot 1.5\text{H}_2\text{O}$

Calcd. C, 61.48 ; H, 6.34 ; N, 4.10

Found. C, 61.50 ; H, 6.11 ; N, 4.09.

35 Working Example 61 (Production of Compound 60)

To a solution of 7-(4-ethoxyphenyl)-N-[4-[[N-

- methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-  
1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
(300mg) in THF (22.5ml) was added at room temperature  
L-(+)-tartaric acid (80mg), and the mixture was stirred at  
5 60°C for 2 hours and concentrated under reduced pressure.  
To the residue was added ethanol, and the mixture was  
concentrated to give crystals, which were collected by  
filtration and washed with ethanol to give colorless  
crystals of 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-  
10 (tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide · 1/2 L-(+)-  
tartarate (Compound 60) (259mg).  
m.p. 245-247 °C (dec.)  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.36 (3H, t, J=7.0 Hz), 1.43-1.66  
15 (2H, m), 1.69-1.82 (2H, m), 2.17 (3H, s), 2.60-2.80 (1H,  
m), 3.04-3.11 (2H, m), 3.17-3.33 (2H, m), 3.62 (2H, s),  
3.75-3.82 (2H, m), 3.87-3.98 (2H, m), 4.10 (2H, q, J=7.0  
Hz), 4.14 (1H, s), 7.07 (2H, d, J=8.9 Hz), 7.30 (2H, d, J=8.5  
Hz), 7.54 (1H, s), 7.69 (2H, d, J=8.5 Hz), 7.76 (2H, d, J=8.9  
20 Hz), 7.87 (1H, dd, J=8.4, 1.8 Hz), 8.04 (1H, d, J=1.8 Hz),  
8.07 (1H, d, J=8.4 Hz), 10.21 (1H, s).  
IR (KBr) 3263, 1659, 1633, 1605, 1518, 1412, 1317, 1294,  
1248, 1128, 825 cm<sup>-1</sup>  
Anal. for C<sub>34</sub>H<sub>39</sub>N<sub>2</sub>O<sub>8</sub>S  
25 Calcd. C, 64.23 ; H, 6.18 ; N, 4.41  
Found. C, 64.21 ; H, 6.19 ; N, 4.63.  
Working Example 62 (Production of Compound 61)  
Under argon atmosphere, to a solution of 4-(4-bromo-3-  
fluorophenyl)morpholine (6.89g) in THF (50ml) was added  
30 dropwise at -78°C a solution of 1.6M n-butyllithium in hexane  
(18.2ml), and the mixture was stirred for 1 hour. To the  
mixture was added dropwise a solution of trimethyl borate  
(9.0ml) in THF (9ml). The reaction mixture was allowed to  
gradually warm to room temperature, and the mixture was  
35 stirred at room temperature for 2 hours. To the mixture was  
added dropwise 1N hydrochloric acid (100ml), and the mixture

was stirred for 30 minutes. To the mixture was added 8N sodium hydroxide solution to make the solution pH 7, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give gray crystals, which were collected by filtration. The crystals were washed with diisopropylether to give gray crystals of 3-fluoro-4-morpholinophenyl borate (0.65g).

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3-fluoro-4-morpholinophenyl borate (156mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate and washed with saturated brine. The extract was heated at 70°C, and crystals were dissolved. The solution was dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and recrystallized from ethanol to give yellow crystals of 7-(3-fluoro-4-morpholinophenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 61) (149mg).  
m.p. 275-277 °C (dec.)  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.64-1.85 (4H, m), 2.22 (3H, s), 2.54-2.77 (1H, m), 3.15-3.19 (6H, m), 3.28-3.44 (2H, m), 3.59 (2H, s), 3.70-3.78 (2H, m), 3.88-3.92 (4H, m), 3.98-4.10 (2H, m), 6.98-7.07 (1H, m), 7.24-7.38 (5H, m), 7.55 (2H, d, J=8.4 Hz), 7.62-7.69 (2H, m), 7.90 (1H, s), 8.21 (1H, d, J=8.0 Hz).  
IR (KBr) 3253, 1657, 1601, 1520, 1315, 1296, 1126 cm<sup>-1</sup>  
Anal. for C<sub>34</sub>H<sub>36</sub>N<sub>3</sub>O<sub>5</sub>SF · 0.6H<sub>2</sub>O  
Calcd. C, 64.76 ; H, 6.27 ; N, 6.66

Found. C, 64.54 ; H, 6.21 ; N, 6.75.

Working Example 63 (Production of Compound 62)

Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
5 yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 3,4-dihydro-2H-1-  
benzopyran-6-yl borate (113mg) and potassium carbonate  
(160mg) in toluene/ethanol/water (10/1/1ml) was stirred at  
room temperature for 1 hour. To the mixture was added  
10 tetrakis(triphenylphosphine)palladium (33mg, 0.029mmol),  
and the mixture was refluxed for 6 hours, cooled, extracted  
with ethyl acetate, washed with saturated brine, dried with  
magnesium sulfate and concentrated under reduced pressure  
to give crystals, which were collected by filtration and  
15 recrystallized from ethanol to give pale yellow crystals  
of 7-(3,4-dihydro-2H-1-benzopyran-6-yl)-N-[4-[[N-  
methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-  
1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide  
(Compound 62) (149mg).

20 m.p. 245-249 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.67-1.83 (4H, m), 1.99-2.11 (2H, m),  
2.21 (3H, s), 2.52-2.75 (1H, m), 2.84-2.90 (2H, m), 3.10-3.21  
(2H, m), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.69-3.74 (2H,  
m), 3.98-4.09 (2H, m), 4.22-4.27 (2H, m), 6.90 (1H, d, J=8.4  
25 Hz), 7.31-7.36 (5H, m), 7.55 (2H, d, J=8.4 Hz), 7.62-7.69  
(2H, m), 7.90 (1H, s), 8.18 (1H, d, J=8.2 Hz).

IR (KBr) 3250, 1653, 1632, 1597, 1529, 1510, 1410, 1317,  
1294, 1128 cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>S

30 Calcd. C, 69.21 ; H, 6.34 ; N, 4.89

Found. C, 68.81 ; H, 6.46 ; N, 4.83.

Working Example 64 (Production of Compound 63)

Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
35 yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 2,3,4,5-

tetrahydro-1-benzoxepin-7-yl borate (122mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the  
5 mixture was refluxed for 7 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:1) to give  
10 crystals, which were recrystallized from ethanol to give colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(2,3,4,5-tetrahydro-1-benzoxepin-7-yl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 63) (231mg).

15 m.p. 238-242 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.68-1.86 (6H, m), 1.94-2.08 (2H, m), 2.22 (3H, s), 2.55-2.76 (1H, m), 2.87-2.92 (2H, m), 3.17 (2H, t, J=6.8 Hz), 3.31-3.44 (2H, m), 3.59 (2H, s), 3.73 (2H, t, J=6.8 Hz), 3.97-4.11 (4H, m), 7.10 (1H, d, J=9.0  
20 Hz), 7.31-7.39 (5H, m), 7.55 (2H, d, J=8.6 Hz), 7.63 (1H, d, J=1.8 Hz), 7.68 (1H, dd, J=8.2, 1.8 Hz), 7.93 (1H, s), 8.20 (1H, d, J=8.2 Hz).

IR (KBr) 3235, 1657, 1635, 1601, 1529, 1510, 1483, 1410, 1316, 1292, 1244, 1125cm<sup>-1</sup>

25 Anal. for C<sub>34</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 69.60 ; H, 6.53 ; N, 4.77

Found. C, 69.31 ; H, 6.53 ; N, 5.01.

Working Example 65 (Production of Compound 64)

Under argon atmosphere, a mixture of 7-bromo-N-[4-  
30 [[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-6-yl borate (131mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was  
35 stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg,

- 0.029mmol), and the mixture was refluxed for 6.5 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and recrystallized from ethanol to give colorless crystals of 7-(2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-6-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 64) (117mg).
- 5 m.p. 222-226 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.37 (6H, s), 1.64-1.82 (4H, m), 1.86 (2H, t, J=6.6 Hz), 2.21 (3H, s), 2.55-2.75 (1H, m), 2.82-2.88 (2H, m), 3.16 (2H, t, J=6.6 Hz), 3.31-3.44 (2H, m), 3.58 (2H, s), 3.68-3.75 (2H, m), 3.98-4.11 (2H, m), 6.89 (1H, d, J=8.8 Hz), 7.30-7.37 (5H, m), 7.55 (2H, d, J=8.4 Hz), 7.61-7.67 (2H, m), 7.93 (1H, s), 8.17 (1H, d, J=8.0 Hz). IR (KBr) 3245, 1653, 1605, 1532, 1514, 1410, 1318, 1302, 1122, 820 cm<sup>-1</sup>
- Anal. for C<sub>33</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S · 0.2H<sub>2</sub>O
- 20 Calcd. C, 69.56 ; H, 6.74 ; N, 4.64  
Found. C, 69.35 ; H, 6.78 ; N, 4.76.
- Working Example 66 (Production of Compound 65)
- Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 4-(2-ethoxyethoxy)-3-fluorophenyl borate (145mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 7 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.
- 25 The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give
- 30  
35

colorless crystals of 7-[4-(2-ethoxyethoxy)-3-fluorophenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 65) (244mg).

5 m.p. 212-214 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.25 (3H, t, J=7.2 Hz), 1.68-1.82 (4H, m), 2.21 (3H, s), 2.54-2.76 (1H, m), 3.14-3.21 (2H, m), 3.30-3.44 (2H, m), 3.58 (2H, s), 3.63 (2H, q, J=7.2 Hz), 3.70-3.76 (2H, m), 3.85 (2H, t, J=4.9 Hz), 3.98-4.10 (2H, m), 4.26 (2H, t, J=4.7 Hz), 7.06-7.15 (1H, m), 7.27-7.39 (5H, m), 7.55 (2H, d, J=8.8 Hz), 7.61-7.67 (2H, m), 7.91 (1H, s), 8.21 (1H, d, J=8.0 Hz).

IR (KBr) 3243, 1651, 1630, 1599, 1526, 1410, 1318, 1294, 1281, 1128 cm<sup>-1</sup>

15 Anal. for C<sub>34</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub>SF

Calcd. C, 65.57 ; H, 6.31 ; N, 4.50

Found. C, 65.28 ; H, 6.18 ; N, 4.50.

Working Example 67 (Production of Compound 66)

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3,4-dihydro-2H-1,5-benzodioxepin-7-yl borate (123mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

30 The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 66) (194mg).



m.p. 242-245 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.66-1.83 (4H, m), 2.21 (3H, s),  
2.18-2.29 (2H, m), 2.55-2.72 (1H, m), 3.13-3.20 (2H, m),  
3.31-3.44 (2H, m), 3.57 (2H, s), 3.68-3.75 (2H, m), 3.98-4.09  
5 (2H, m), 4.26-4.31 (4H, m), 7.06 (1H, d, J=8.4 Hz), 7.17  
(1H, dd, J=8.8, 2.2 Hz), 7.23 (1H, d, J=2.2 Hz), 7.30-7.35  
(3H, m), 7.54 (2H, d, J=8.4 Hz), 7.60-7.67 (2H, m), 7.83  
(1H, s), 8.19 (1H, d, J=8.4 Hz).

IR (KBr) 3248, 1651, 1632, 1601, 1532, 1510, 1410, 1317,  
10 1298, 1267, 1125 cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 67.33 ; H, 6.16 ; N, 4.76

Found. C, 66.96 ; H, 6.32 ; N, 4.74.

Working Example 68 (Production of Compound 67)

15 Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 3-chloro-4-(2-  
ethoxyethoxy)phenyl borate (156mg) and potassium carbonate  
20 (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at  
room temperature for 1 hour. To the mixture was added  
tetrakis(triphenylphosphine)palladium (33mg), and the  
mixture was refluxed for 6 hours, cooled, extracted with  
ethyl acetate, washed with saturated brine, dried with  
25 magnesium sulfate and concentrated under reduced pressure.

The residue was purified with silica gel column  
chromatography (ethanol/ethyl acetate=1:3) and  
recrystallized from ethanol to give colorless crystals of  
7-[3-chloro-4-(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-  
30 N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-  
2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 67)  
(269mg).

m.p. 203-205 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J=7.1 Hz), 1.68-1.82 (4H,  
35 m), 2.21 (3H, s), 2.55-2.76 (1H, m), 3.14-3.21 (2H, m),  
3.31-3.44 (2H, m), 3.58 (2H, s), 3.66 (2H, q, J=7.1 Hz),

- 3.69-3.76 (2H, m), 3.85-3.90 (2H, m), 3.99-4.10 (2H, m), 4.23-4.28 (2H, m), 7.07 (1H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.45 (1H, dd, J=8.8, 2.2 Hz), 7.54 (2H, d, J=8.4 Hz), 7.61-7.68 (3H, m), 7.78 (1H, s), 8.21 (1H, d, J=8.2 Hz).
- 5 IR (KBr) 3250, 1651, 1632, 1601, 1527, 1510, 1482, 1410, 1318, 1294, 1273, 11300  $\text{cm}^{-1}$
- Anal. for  $\text{C}_{34}\text{H}_{39}\text{N}_2\text{O}_6\text{SCl}$
- Calcd. C, 63.89 ; H, 6.15 ; N, 4.38
- Found. C, 63.73 ; H, 6.19 ; N, 4.39.
- 10 Working Example 69 (Production of Compound 68)
- Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 4-
- 15 (tetrahydropyran-4-yloxy)phenyl borate (141mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled,
- 20 extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give
- 25 colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(tetrahydropyran-4-yloxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 68) (274mg). m.p. 227-229  $^{\circ}\text{C}$
- 30  $^1\text{H}$ -NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.63-1.92 (6H, m), 1.99-2.15 (2H, m), 2.21 (3H, s), 2.55-2.76 (1H, m), 3.13-3.21 (2H, m), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.59-3.75 (4H, m), 3.95-4.11 (4H, m), 4.50-4.63 (1H, m), 7.03 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.52-7.56 (4H, m), 7.62-7.68 (2H, m), 7.79 (1H, s), 8.20 (1H, d, J=8.0 Hz).
- 35 IR (KBr) 3243, 1655, 1638, 1603, 1518, 1410, 1316, 1292,

1250, 1130  $\text{cm}^{-1}$

Anal. for  $\text{C}_{35}\text{H}_{40}\text{N}_2\text{O}_5\text{S}$

Calcd. C, 68.16 ; H, 6.54 ; N, 4.54

Found. C, 67.95 ; H, 6.57 ; N, 4.56.

5 Working Example 70 (Production of Compound 69)

Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 4-[N-(2-  
10 ethoxyethyl)-N-ethylamino]phenyl borate (410mg) and  
potassium carbonate (400mg) in toluene/ethanol/water  
(10/1/1ml) was stirred at room temperature for 1 hour. To  
the mixture was added tetrakis(triphenylphosphine)palladium  
(50mg), and the mixture was refluxed for 8 hours, cooled,  
15 extracted with ethyl acetate, washed with saturated brine,  
dried with magnesium sulfate and concentrated under reduced  
pressure. The residue was purified with silica gel column  
chromatography (ethanol/ethyl acetate=1:3) to give  
crystals, which were recrystallized from ethanol to give  
20 yellow crystals of 7-[4-[N-(2-ethoxyethyl)-N-  
ethylamino]phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-  
4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (Compound 69) (260mg).  
m.p. 194-197  $^{\circ}\text{C}$

25  $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.21 (3H, t,  $J=7.0$  Hz), 1.22 (3H, t,  
 $J=7.0$  Hz), 1.68-1.83 (4H, m), 2.21 (3H, s), 2.52-2.73 (1H,  
m), 3.15 (2H, t,  $J=6.8$  Hz), 3.31-3.64 (12H, m), 3.71 (2H,  
t,  $J=6.8$  Hz), 3.98-4.10 (2H, m), 6.77 (2H, d,  $J=9.2$  Hz),  
7.30-7.34 (3H, m), 7.47-7.66 (6H, m), 7.90 (1H, s), 8.13  
30 (1H, d,  $J=8.4$  Hz).

IR (KBr) 3281, 1655, 1637, 1607, 1591, 1526, 1412, 1318,  
1294, 1128, 810  $\text{cm}^{-1}$

Anal. for  $\text{C}_{36}\text{H}_{45}\text{N}_3\text{O}_5\text{S} \cdot 0.3\text{H}_2\text{O}$

Calcd. C, 67.86 ; H, 7.21 ; N, 6.59

35 Found. C, 67.74 ; H, 6.91 ; N, 6.67.

Working Example 71 (Production of Compound 70)

- Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (300mg), 4-[N-(2-  
ethoxyethyl)-N-methylamino]phenyl borate (168mg) and  
potassium carbonate (176mg) in toluene/ethanol/water  
(10/1/1ml) was stirred at room temperature for 1 hour. To  
the mixture was added tetrakis(triphenylphosphine)palladium  
(33mg), and the mixture was refluxed for 8 hours, cooled,  
extracted with ethyl acetate, washed with saturated brine,  
dried with magnesium sulfate and concentrated under reduced  
pressure. The residue was purified with silica gel column  
chromatography (ethanol/ethyl acetate=1:3) to give  
crystals, which were recrystallized from ethanol to give  
yellow crystals of 7-[4-[N-(2-ethoxyethyl)-N-  
methylamino]phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-  
4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (Compound 70) (235mg).  
m.p. 190-192 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.20 (3H, t, J=7.0 Hz), 1.67-1.84 (4H, m), 2.21 (3H, s), 2.55-2.75 (1H, m), 3.06 (3H, s), 3.15 (2H, t, J=6.6 Hz), 3.31-3.44 (2H, m), 3.46-3.63 (8H, m), 3.68-3.74 (2H, m), 3.99-4.09 (2H, m), 6.80 (2H, d, J=9.0 Hz), 7.30-7.35 (3H, m), 7.49-7.67 (6H, m), 7.87 (1H, s), 8.14 (1H, d, J=8.0 Hz).
- IR (KBr) 3275, 1655, 1636, 1609, 1591, 1526, 1508, 1318, 1292, 1128, 810 cm<sup>-1</sup>
- Anal. for C<sub>35</sub>H<sub>43</sub>N<sub>3</sub>O<sub>3</sub>S  
Calcd. C, 68.04 ; H, 7.02 ; N, 6.80  
Found. C, 67.68 ; H, 6.72 ; N, 6.89.

Working Example 72 (Production of Compound 71)

- Under argon atmosphere, a mixture of 7-bromo-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (200mg), 4-[N-ethyl-N-(2-  
propoxyethyl)amino]phenyl borate (290mg) and potassium

carbonate (266mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (40mg), and the mixture was refluxed for 8 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and was concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give pale yellow crystals of 7-[4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 71) (89mg).

m.p. 172-175 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.3 Hz), 1.21 (3H, t, J=7.0 Hz), 1.53-1.83 (6H, m), 2.21 (3H, s), 2.55-2.74 (1H, m), 3.12-3.19 (2H, m), 3.31-3.63 (12H, m), 3.68-3.74 (2H, m), 3.99-4.11 (2H, m), 6.77 (2H, d, J=9.0 Hz), 7.30-7.35 (3H, m), 7.48-7.69 (6H, m), 7.88 (1H, s), 8.14 (1H, d, J=8.2 Hz).

IR (KBr) 3281, 1655, 1607, 1590, 1524, 1410, 1318, 1294, 1128, 810 cm<sup>-1</sup>

Anal. for C<sub>37</sub>H<sub>47</sub>N<sub>3</sub>O<sub>5</sub>S

Calcd. C, 68.81 ; H, 7.33 ; N, 6.51

Found. C, 68.77 ; H, 7.25 ; N, 6.60.

Working Example 73 (Production of Compound 72)

Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 4-[N-methyl-N-(2-propoxyethyl)amino]phenyl borate (205mg) and potassium carbonate (176mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (40mg), and the mixture was refluxed for 8 hours, cooled, extracted with

ethyl acetate, washed with saturated brine, dried with magnesium sulfate and was concentrated under reduced pressure. The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:4) to give  
5 crystals, which were recrystallized from ethanol to give pale yellow crystals of 7-[4-[N-methyl-N-(2-propoxyethyl)amino]phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 72)  
10 (210mg).

m.p. 193-194 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.91 (3H, t, J=7.4 Hz), 1.53-1.83 (6H, m), 2.21 (3H, s), 2.53-2.76 (1H, m), 3.07 (3H, s), 3.16 (2H, t, J=6.8 Hz), 3.31-3.44 (4H, m), 3.58-3.62 (6H, m), 3.68-3.75  
15 (2H, m), 3.99-4.12 (2H, m), 6.80 (2H, d, J=9.0 Hz), 7.31-7.35 (3H, m), 7.50-7.57 (4H, m), 7.61 (1H, d, J=1.7 Hz), 7.66 (1H, dd, J=8.3, 1.7 Hz), 7.87 (1H, s), 8.15 (1H, d, J=8.3 Hz).

IR (KBr) 3281, 1655, 1638, 1609, 1591, 1526, 1410, 1318,  
20 1294, 1128, 810 cm<sup>-1</sup>

Anal. for C<sub>36</sub>H<sub>45</sub>N<sub>3</sub>O<sub>5</sub>S

Calcd. C, 68.43 ; H, 7.18 ; N, 6.65

Found. C, 68.50 ; H, 7.18 ; N, 6.79.

Working Example 74 (Production of Compound 73)

25 Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3-ethoxy-4-(2-propoxyethoxy)phenyl borate (171mg) and potassium  
30 carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with  
35 magnesium sulfate and was concentrated under reduced pressure. The residue was purified with silica gel column

- chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-[3-ethoxy-4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 73) (237mg).
- m.p. 171-172 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J=7.3 Hz), 1.47 (3H, t, J=7.0 Hz), 1.58-1.83 (6H, m), 2.21 (3H, s), 2.56-2.73 (1H, m), 3.14-3.21 (2H, m), 3.30-3.45 (2H, m), 3.52 (2H, t, J=6.8 Hz), 3.58 (2H, s), 3.68-3.75 (2H, m), 3.85 (2H, t, J=4.9 Hz), 3.99-4.10 (2H, m), 4.16 (2H, q, J=7.0 Hz), 4.23 (2H, t, J=4.9 Hz), 7.01 (1H, d, J=8.0 Hz), 7.10-7.15 (2H, m), 7.31-7.35 (3H, m), 7.55 (2H, d, J=8.4 Hz), 7.59 (1H, d, J=2.0 Hz), 7.64 (1H, dd, J=8.0, 2.0 Hz), 7.86 (1H, s), 8.18 (1H, d, J=8.0 Hz).
- IR (KBr) 3324, 1651, 1595, 1520, 1316, 1291, 1254, 1128, 810 cm<sup>-1</sup>
- Anal. for C<sub>37</sub>H<sub>46</sub>N<sub>2</sub>O<sub>7</sub>S  
 Calcd. C, 67.04 ; H, 6.99 ; N, 4.23  
 Found. C, 66.75 ; H, 7.02 ; N, 4.22.
- Working Example 75 (Production of Compound 74)
- Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3-chloro-4-(2-propoxyethoxy)phenyl borate (164mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 6 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure to give crystals, which were collected by filtration and recrystallized from ethanol to give colorless crystals of

7-[3-chloro-4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 74) (255mg).

5 m.p. 183-184 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.4 Hz), 1.54-1.82 (6H, m), 2.21 (3H, s), 2.55-2.72 (1H, m), 3.14-3.20 (2H, m), 3.31-3.44 (2H, m), 3.55 (2H, t, J=6.8 Hz), 3.57 (2H, s), 3.69-3.75 (2H, m), 3.87 (2H, t, J=4.9 Hz), 3.99-4.09 (2H, m), 4.26 (2H, t, J=4.9 Hz), 7.07 (1H, d, J=8.6 Hz), 7.30-7.35 (3H, m), 7.45 (1H, dd, J=8.6, 2.4 Hz), 7.54 (2H, d, J=8.4 Hz), 7.60-7.67 (3H, m), 7.82 (1H, s), 8.20 (1H, d, J=8.0 Hz).

10 IR (KBr) 3241, 1651, 1634, 1601, 1507, 1410, 1318, 1294, 15 1130 cm<sup>-1</sup>

Anal. for C<sub>35</sub>H<sub>41</sub>N<sub>2</sub>O<sub>6</sub>SCl

Calcd. C, 64.35 ; H, 6.33 ; N, 4.29

Found. C, 64.24 ; H, 6.38 ; N, 4.25.

Working Example 76 (Production of Compound 75)

20 Under argon atmosphere, a mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg), 3-methyl-4-(2-propoxyethoxy)phenyl borate (151mg) and potassium carbonate (160mg) in toluene/ethanol/water (10/1/1ml) was stirred at room temperature for 1 hour. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was refluxed for 8 hours, cooled, extracted with ethyl acetate, washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure.

30 The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:3) to give crystals, which were recrystallized from ethanol to give colorless crystals of 7-[3-methyl-4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-



2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 75)  
(261mg).

m.p. 192-195 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.3 Hz), 1.56-1.83 (6H, m), 2.21 (3H, s), 2.31 (3H, s), 2.54-2.74 (1H, m), 3.16 (2H, t, J=6.6 Hz), 3.30-3.45 (2H, m), 3.53 (2H, t, J=6.6 Hz), 3.57 (2H, s), 3.72 (2H, t, J=6.6 Hz), 3.82-3.87 (2H, m), 3.98-4.09 (2H, m), 4.16-4.21 (2H, m), 6.93 (1H, d, J=9.2 Hz), 7.30-7.43 (5H, m), 7.54 (2H, d, J=8.4 Hz), 7.62-7.68 (2H, m), 7.85 (1H, s), 8.18 (1H, d, J=8.4 Hz).

IR (KBr) 3279, 1661, 1603, 1534, 1514, 1313, 1291, 1254, 1132 cm<sup>-1</sup>

Anal. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 68.33 ; H, 7.01 ; N, 4.43

Found. C, 68.30 ; H, 6.92 ; N, 4.45.

Working Example 77 (Production of Compound 76)

To a solution of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (17.6g) in THF (1160ml) was added at room temperature 6N hydrochloric acid (10ml), and the mixture was stirred for 2 hours. Precipitated crystals were collected by filtration and washed with THF and diisopropylether to give colorless crystals, which were recrystallized from ethanol/water to give colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide hydrochloride (Compound 76) (13.2g).

m.p. 259-273 °C (dec.)

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.00 (3H, t, J=7.3 Hz), 1.67-1.91 (4H, m), 1.94-2.16 (2H, m), 2.57-2.59 (3H, m), 3.01-3.12 (2H, m), 3.21-3.51 (3H, m), 3.76-3.83 (2H, m), 3.97-4.19 (5H, m), 4.37-4.48 (1H, m), 7.08 (2H, d, J=8.8 Hz), 7.56-7.60 (3H, m), 7.74-7.90 (5H, m), 8.05-8.09 (2H, m), 10.23-10.39 (1H, m), 10.44 (1H, s).

IR (KBr) 3218, 1669, 1595, 1522, 1319, 1294, 1258, 1168, 1132, 831  $\text{cm}^{-1}$

Anal. for  $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_5\text{SCl}$

Calcd. C, 64.85 ; H, 6.43 ; N, 4.58 ; Cl, 5.80

5 Found. C, 64.84 ; H, 6.50 ; N, 4.34 ; Cl, 5.61

Working Example 78 (Production of Compound 77)

To a suspension of 7-(4-ethoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg) in THF (5ml) were added at room temperature thionyl chloride  
10 (0.05ml) and a drop of DMF, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the residue was dissolved in THF (10ml). The solution was added dropwise at room temperature to a suspension of 4-[[N-(3-ethoxypropyl)-N-methylamino]methyl]aniline  
15 dihydrochloride (181mg) and triethylamine (0.39ml) in THF (2ml), and the mixture was stirred for 4 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under  
20 reduced pressure. The residue was purified with silica gel column chromatography (ethanol/ethyl acetate=1:2) and recrystallized from ethanol to give colorless crystals of 7-(4-ethoxyphenyl)-N-[4-[[N-(3-ethoxypropyl)-N-methylamino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
25 benzothiepine-4-carboxamide (Compound 77) (161mg).  
m.p. 197-198  $^{\circ}\text{C}$

$^1\text{H}$ -NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.19 (3H, t,  $J=7.0$  Hz), 1.45 (3H, t,  $J=7.0$  Hz), 1.73-1.88 (2H, m), 2.19 (3H, s), 2.45 (2H, t,  $J=7.4$  Hz), 3.16 (2H, t,  $J=6.8$  Hz), 3.42-3.52 (6H, m), 3.71  
30 (2H, t,  $J=6.8$  Hz), 4.10 (2H, q,  $J=7.0$  Hz), 7.00 (2H, d,  $J=8.8$  Hz), 7.29-7.34 (3H, m), 7.53 (2H, d,  $J=8.8$  Hz), 7.54 (2H, d,  $J=8.4$  Hz), 7.60 (1H, d,  $J=1.8$  Hz), 7.65 (1H, dd,  $J=8.0$ , 1.8 Hz), 7.95 (1H, br s), 8.18 (1H, d,  $J=8.0$  Hz).

IR (KBr) 3338, 1651, 1606, 1518, 1311, 1292, 1252, 1165,  
35 1128, 820  $\text{cm}^{-1}$

Anal. for  $\text{C}_{32}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$

Calcd. C, 68.30 ; H, 6.81 ; N, 4.98

Found. C, 68.20 ; H, 6.75 ; N, 4.93.

Reference Example 95

In DMF (100ml) was dissolved 4-bromobenzenethiol  
5 (10.0g), and to the mixture was added at room temperature  
potassium carbonate (9.5g). To the mixture was added  
dropwise 1-iodopentane (8.3ml), and the mixture was stirred  
for 2 hours. The reaction mixture was added to water, and  
the mixture was extracted with ethyl acetate, washed with  
10 saturated brine and dried with magnesium sulfate. Under  
reduced pressure, the solvent was evaporated, and the  
residue was dissolved in THF (112ml). To the solution was  
added dropwise at -78°C 1.6M n-butyllithium/hexane (32.9ml),  
and the mixture was stirred for 1 hour. To the mixture was  
15 added dropwise a solution of trimethyl borate (14.9g) in  
THF (30ml), and the mixture was stirred for 30 minutes and  
warmed to room temperature. To the mixture was added 10%  
sulfuric acid (61ml), and the mixture was stirred for 15  
minutes. The reaction solution was extracted with ethyl  
20 acetate, washed with saturated brine and dried with  
magnesium sulfate. Under reduced pressure, the solvent was  
evaporated, and the residue was washed with  
hexane/isopropylether to give 4-(pentylthio)phenyl borate  
(5.6g).  
25 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.0Hz), 1.23-1.52 (4H,  
m), 1.65-1.81 (2H, m), 3.01 (2H, t, J=7.4Hz), 7.38 (2H, d,  
J=8.4Hz), 8.10 (2H, d, J=8.4Hz)

Working Example 79 (Production of Compound 78)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-  
30 yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (310mg) was added  
toluene/ethanol/water (10/1/1, 6.0ml) and then were added  
4-(pentylthio)phenyl borate (182mg) and potassium  
carbonate (181mg), and the mixture was stirred at room  
35 temperature for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (34mg), and the

mixture was stirred at 100°C for 12 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under  
5 reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-pentylthiophenyl)-1,1-  
10 dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 78) (161mg).

m.p. 204-206°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.91 (3H, t, J=7.0Hz), 1.23-1.49 (4H, m), 1.62-1.76 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 2.98 (2H, t, J=7.4Hz), 3.12-3.20 (2H, m), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.68-3.75 (2H, m), 4.00-4.08 (2H, m), 7.29-7.41 (5H, m), 7.48-7.68 (6H, m), 8.00 (1H, s), 8.20 (1H, d, J=8.0Hz)  
15 IR(KBr) 3252, 2951, 1653, 1597, 1526, 1410, 1317, 1294, 1130, 814cm<sup>-1</sup>

20 Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>

Calcd. C, 67.93 ; H, 6.84 ; N, 4.53

Found. C, 67.84 ; H, 6.84 ; N, 4.52

Reference Example 96

In DMF (100ml) was dissolved 4-bromobenzenethiol  
25 (10.1g), and to the solution was added at room temperature potassium carbonate (9.6g). To the mixture was added dropwise 1-iodohexane (9.5ml), and the mixture was stirred for 2 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with  
30 saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give 1-bromo-4-(hexylthio)benzene (14.2g). In THF (127ml) was dissolved  
35 1-bromo-4-(hexylthio)benzene (14.1g), and to the solution was added dropwise at -78°C 1.6M n-butyllithium/hexane

(35.5ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (16.1g) in THF (32ml), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 10% sulfuric acid (70.5ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(hexylthio)phenyl borate (6.6g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.90 (3H, t, J=6.4Hz), 1.26-1.76 (8H, m), 3.01 (2H, t, J=7.37 (2H, d, J=8.0Hz), 8.09 (2H, d, J=8.0Hz)

Working Example 80 (Production of Compound 79)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (320mg) was added toluene/ethanol/water (10/1/1, 12ml) and then were added 4-(hexylthio)phenyl borate (199mg) and potassium carbonate (187mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (36mg), and the mixture was stirred at 100°C for 14 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(4-hexylthiophenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 79) (298mg).

m.p. 205-207°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.90 (3H, t, J=6.4Hz), 1.30-1.50 (4H,

m), 1.62-1.76 (6H, m), 2.20 (3H, s), 3.31-3.44 (2H, m), 3.56 (2H, s), 3.66-3.74 (2H, m), 4.00-4.08 (2H, m), 7.28-7.40 (5H, m), 7.46-7.66 (6H, m), 8.04 (1H, s), 8.18 (1H, d, J=8.0Hz)

- 5 IR(KBr) 3275, 2951, 1655, 1597, 1526, 1410, 1318, 1294, 1130, 814 $\text{cm}^{-1}$

Anal. for  $\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_4\text{S}_2$

Calcd. C, 68.32 ; H, 7.01 ; N, 4.43

Found. C, 68.35 ; H, 7.13 ; N, 4.47

- 10 Reference Example 97

In THF (200ml) was dissolved 4-bromobenzyl alcohol (19.8g), and to the solution was added under ice-cooling 65% sodium hydride (3.6g). The mixture was stirred at room temperature for 30 minutes, and to the mixture was added  
15 dropwise under ice-cooling iodomethane (8.0ml). The mixture was stirred at room temperature for 2 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure,  
20 the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=12/1) to give 1-bromo-4-(methoxymethyl)benzene (14.8g). In THF (110ml) was dissolved 1-bromo-4-(methoxymethyl)benzene (12.8g), and to the mixture was added  
25 dropwise at  $-78^\circ\text{C}$  1.6M n-butyllithium/hexane (42.4ml). The mixture was stirred for 1 hour, and to the mixture was added dropwise a solution of trimethyl borate (19.2g) in THF (38.4ml). The mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 5% sulfuric  
30 acid (124ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give  
35 4-(methoxymethyl)phenyl borate (6.3g).

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  3.09 (3H, s), 4.41 (2H, s), 7.27 (2H,

d, J=8.0Hz), 7.77 (2H, d, J=8.0Hz)

Working Example 81 (Production of Compound 80)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (220mg) was added toluene/ethanol/water (10/1/1, 6ml) and then were added 4-(methoxymethyl)phenyl borate (86mg) and potassium carbonate (123mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (19mg), and the mixture was stirred at 90°C for 9 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(4-methoxymethylphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 80) (99mg).

m.p. 227-229°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.60-1.82 (4H, m), 2.21 (3H, s), 2.66 (1H, m), 3.13-3.22 (2H, m), 3.30-3.45 (2H, m), 3.44 (3H, s), 3.69-3.78 (2H, m), 4.00-4.08 (2H, m), 4.53 (2H, s), 7.26-7.38 (3H, m), 7.44-7.74 (8H, m), 7.92 (1H, s), 8.23 (1H, d, J=8.0Hz)

IR(KBr) 3239, 29198, 2840, 1655, 1601, 1530, 1412, 1318, 1294, 1130, 816cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 68.55 ; H, 6.47 ; N, 5.00

Found. C, 68.37 ; H, 6.38 ; N, 5.05

Reference Example 98

In THF (100ml) was dissolved 4-bromophenethyl alcohol (10g). To the mixture was added under ice-cooling 65% sodium hydride (1.7g), and the mixture was stirred at room

temperature for 30 minutes. To the mixture was added dropwise under ice-cooling iodomethane (3.7ml), and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was added to water, and the mixture was  
5 extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=6/1) to give 1-bromo-4-(2-methoxyethyl)benzene  
10 (8.3g). In THF (100ml) was dissolved 1-bromo-4-(2-methoxyethyl)benzene (8.2g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (26.0ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (11.8g) in THF (12ml),  
15 and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 10% sulfuric acid (40ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate.  
20 Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(2-methoxyethyl)phenyl borate (3.7g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.98 (2H, t, J=6.8Hz), 3.38 (3H, s), 3.67 (2H, t, J=6.8Hz), 7.37 (2H, d, J=7.6Hz), 8.16 (2H, d, J=7.6Hz)  
25

Working Example 82 (Production of Compound 81)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (420mg) was added  
30 toluene/ethanol/water (10/1/1, 16.2ml) and then were added 4-(2-methoxyethyl)phenyl borate (216mg) and potassium carbonate (245mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the  
35 mixture was stirred at 100°C for 10 hours and cooled to room temperature. The mixture was added to water, and the



mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(2-methoxyethyl)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 81) (99mg).

m.p. 216-219°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.61-1.83 (4H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13-3.20 (2H, m), 3.30-3.43 (2H, m), 3.38 (3H, s), 3.58 (2H, m), 3.66 (2H, s), 3.65-3.76 (2H, m), 3.98-4.08 (2H, m), 7.30-7.38 (6H, m), 7.51-7.57 (4H, m), 7.98 (1H, s), 8.20 (1H, d, J=8.2Hz)

IR(KBr) 3293, 2944, 1667, 1597, 1522, 1408, 1314, 1294, 1130, 735cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 68.96 ; H, 6.66 ; N, 4.87

Found. C, 68.85 ; H, 6.62 ; N, 4.83

Reference Example 99

To methyl 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylate (960mg) were added THF (19.2ml), methanol (9.6ml) and 1N sodium hydroxide (3.4ml), and the mixture was stirred at room temperature for 3 hours.

Under reduced pressure, the organic solvent was evaporated.

To the residue was added ethyl acetate, and the mixture was extracted with water. To the mixture was added 6N hydrochloric acid (2ml), and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (850mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.35 (3H, t, J=7.0Hz), 2.85-2.92 (2H, m), 3.14-3.20 (2H, m), 4.07 (2H, q, J=7.0Hz), 7.00 (2H, d, J=8.6Hz), 7.48 (2H, s), 7.65 (2H, d, J=8.6Hz), 7.79 (2H,

d, J=9.6Hz)

Reference Example 100

In THF (15.3ml) was dissolved 7-(4-ethoxyphenyl)-2,3-dihydro-1-benzothiepine-4-carboxylic acid (510mg).

- 5 To the mixture were added under ice-cooling thionyl chloride (0.11ml) and DMF (one drop), and the mixture was stirred at room temperature for 1 hour. To a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (389mg) and triethylamine (0.87ml) in THF (15.3ml) was added  
10 the reaction mixture, and the mixture was stirred at room temperature for 2 hours. The reaction mixture added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the  
15 residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) to give 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (512mg).

- 20 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.44 (3H, t, J=7.0Hz), 1.63-1.86 (4H, m), 2.21 (3H, s), 2.67 (1H, m), 3.02-3.09 (2H, m), 3.24-3.44 (4H, m), 3.59 (2H, m), 4.00-4.10 (2H, m), 4.08 (2H, q, J=7.0Hz), 6.93-7.00 (2H, m), 7.29-7.58 (10H, m), 7.79 (1H, s)

25 Reference Example 101

- In THF (15ml) was dissolved 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg). To the mixture was added dropwise at  
30 -78°C a solution of m-chloroperbenzoic acid (140mg) in THF (15ml), and the mixture was stirred at -78°C for 30 minutes and added to an aqueous solution of saturated sodium thiosulfate. To the mixture was added saturated sodium bicarbonate solution, and the mixture was extracted with  
35 ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was

evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1→2/1, 1% triethylamine) to give 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-oxide-(tetrahydropyran-4-

5 yl)amino]methyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (140mg).

m.p. 122-126°C.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.44 (3H, t, J=7.0Hz), 1.80-2.01 (4H, m), 3.25 (3H, s), 3.03-3.10 (2H, m), 3.21-3.40 (4H, m), 3.74  
10 (1H, m), 3.98-4.10 (2H, m), 4.07 (2H, q, J=7.0Hz), 4.34 (2H, s), 6.96 (2H, d, J=8.6Hz), 7.29-7.55 (8H, m), 7.73 (2H, d, J=8.6Hz), 8.87 (1H, s)

Working Example 83 (Production of Compound 82)

In THF (5.2ml) was dissolved 7-(4-ethylthiophenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (260mg). To the mixture were added at room temperature thionyl chloride (0.06ml) and DMF (one drop), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added dropwise to a  
20 solution of 4-[[N-(3-ethoxypropyl)-N-methylamino]methyl]aniline (0.58ml) in THF (5.2ml), and the mixture was stirred at room temperature for 2 hours. The reaction mixture added to water, and the mixture was  
25 extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to  
30 give 7-(4-ethylthiophenyl)-N-[4-[[N-(3-ethoxypropyl)-N-methylamino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 82) (115mg).

m.p. 176-179°C.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.20 (3H, t, J=7.0Hz), 1.37 (3H, t, J=7.4Hz), 1.58-1.78 (2H, m), 2.20 (3H, s), 2.47 (3H, t, J=7.4Hz), 3.02 (2H, q, J=7.4Hz), 3.13-3.21 (2H, m),  
35 3.42-3.53 (2H, m), 3.69-3.76 (2H, m), 7.29-7.71 (11H, m),

7.97 (1H, s), 8.21 (1H, d, J=8.0Hz)

IR(KBr) 3349, 2974, 1669, 1593, 1520, 1406, 1308, 1128, 816cm<sup>-1</sup>

Anal. for C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>

5 Calcd. C, 66.41 ; H, 6.62 ; N, 4.84

Found. C, 66.55 ; H, 6.64 ; N, 4.94

Working Example 84 (Production of Compound 83)

In methylene chloride (6ml) was dissolved 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzothiepine-4-carboxamide (199mg). To the mixture was added at -30°C m-chloroperbenzoic acid (93mg), and the mixture was stirred at -30°C for 30 minutes and added to an aqueous solution of saturated sodium thiosulfate. To the mixture was added saturated sodium bicarbonate solution, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol =3/1→2/1, 1%triethylamine) to give 7-(4-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-oxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 83) (28mg). m.p. 192-195°C.

25 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45 (3H, t, J=7.0Hz), 1.66-2.10 (4H, m), 2.26 (3H, s), 2.60-2.92 (3H, m), 3.10-3.21 (2H, m), 3.31-3.44 (2H, m), 3.65 (2H, s), 3.81-3.95 (2H, m), 4.02-4.10 (2H, m), 4.08 (2H, q, J=7.0Hz), 6.95 (2H, d, J=8.8Hz), 7.34-7.71 (9H, m), 7.95 (1H, d, J=8.2Hz), 8.33-8.36 (1H, m)

IR(KBr) 3247, 2944, 1659, 1607, 1518, 1248, 1020, 814cm<sup>-1</sup>

Reference Example 102

In DMF (80ml) was dissolved 4-bromophenol (10g). To the mixture was added at room temperature potassium carbonate (16.0g) and then were added 2-chloroethylethyl ether (8.3ml) and sodium iodide (9.53g), and the mixture

was stirred at 90°C for 5 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with 1N sodium hydroxide and saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give 1-bromo-4-(2-ethoxyethoxy)benzene (10.7g). In THF (100ml) was dissolved 1-bromo-4-(2-ethoxyethoxy)benzene (10.3g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (29.1ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (13.2g) in THF (13ml), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 10% sulfuric acid (50ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(2-ethoxyethoxy)phenyl borate (2.52g). <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.13 (3H, t, J=7.0Hz), 3.50 (2H, q, J=7.0Hz), 3.66-3.71 (2H, m), 4.06-4.11 (2H, m), 6.89 (2H, d, J=8.4Hz), 7.14 (2H, d, J=8.4Hz)

Working Example 85 (Production of Compound 84)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (350mg) was added toluene/ethanol/water (10/1/1, 13.6ml) and then were added 4-(2-ethoxyethoxy)phenyl borate (226mg) and potassium carbonate (205mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (40mg), and the mixture was stirred at 100°C for 9 hours and cooled to room temperature. The mixture was added to water and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced

pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 84) (312mg).

m.p. 215-217°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J=7.0Hz), 1.60-1.81 (4H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13-3.21 (2H, m), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.63 (2H, q, J=7.0Hz), 3.67-3.75 (2H, m), 3.83 (2H, t, J=5.0Hz), 3.98-4.09 (2H, m), 4.19 (2H, t, J=5.0Hz), 7.24 (2H, d, J=8.8Hz), 7.30 (1H, s), 7.35 (1H, s), 7.51-7.69 (6H, m), 7.81 (1H, s), 8.19 (1H, d, J=8.4Hz)  
IR(KBr) 3243, 2948, 1655, 1607, 1520, 1412, 1294, 1254, 1130, 824cm<sup>-1</sup>

Anal. for C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 67.53 ; H, 6.67 ; N, 4.63

Found. C, 67.55 ; H, 6.58 ; N, 4.71

#### 20 Reference Example 103

In DMF (120ml) was dissolved 4-bromophenol (15g). To the mixture was added at room temperature potassium carbonate (21.6g) and then were added 2-chloroethylmethylsulfide (10ml) and sodium iodide (15.6g), and the mixture was stirred at 90°C for 16 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 1-bromo-4-(2-methylthioethoxy)benzene (4.0g). In THF (58ml) was dissolved 1-bromo-4-(2-methylthioethoxy)benzene (3.9g).

To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (10ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of

trimethyl borate (4.6g) in THF (9.3ml), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 10% sulfuric acid (20ml), and the mixture was stirred for 15 minutes. The reaction mixture  
5 was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(2-methylthioethoxy)phenyl borate (1.39g).  
10 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.25 (3H, s), 2.93 (2H, t, J=6.8Hz), 4.25 (2H, t, J=6.8Hz), 7.01 (2H, d, J=8.8Hz), 8.16 (2H, d, J=8.8Hz)

Working Example 86 (Production of Compound 85)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (360mg) was added  
15 toluene/ethanol/water (10/1/1, 14.2ml) and then were added 4-(2-methylthioethoxy)phenyl borate (241mg) and potassium carbonate (216mg), and the mixture was stirred at room  
20 temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (41mg), and the mixture was stirred at 100°C for 10 hours and cooled to room temperature. The mixture was added to water, and the  
25 mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from  
30 ethanol to give 7-[4-(2-methylthioethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 85) (30mg).  
m.p. 222-224°C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.66-1.76 (4H, m), 2.21 (3H, s), 2.24  
35 (3H, s), 2.65 (1H, m), 2.92 (2H, t, J=6.6Hz), 3.12-3.20 (2H, m), 3.37 (2H, m), 3.57 (2H, s), 3.68-3.75 (2H, m), 3.87-4.01

(2H, m), 4.22 (2H, t, J=6.6Hz), 7.02 (2H, d, J=8.8Hz),  
7.30-7.35 (2H, m), 7.51-7.67 (7H, m), 7.97 (1H, s), 8.18  
(1H, d, J=8.0Hz)

IR(KBr) 3291, 2959, 1655, 1603, 1520, 1412, 1294, 1252, 1130,  
5 824cm<sup>-1</sup>

#### Reference Example 104

In DMF (255ml) was dissolved 4-bromophenol (51.0g).  
To the mixture was added at room temperature potassium  
carbonate (81.5g) and then was added dropwise  
10 chloromethylmethyl ether (44.8ml), and the mixture was  
stirred for 2 hours. The reaction mixture was added to water,  
and the mixture was extracted with ethyl acetate, washed  
with saturated brine and dried with magnesium sulfate.  
Under reduced pressure, the solvent was evaporated, and the  
15 residue was purified with silica gel column chromatography  
(hexane/ethyl acetate=8/1) to give 1-bromo-4-  
(methoxymethoxy)benzene (61.4g). In ether (240ml) was  
dissolved 1-bromo-4-(methoxymethoxy)benzene (30g). To the  
mixture was added dropwise at -78°C 1.6M n-  
20 butyllithium/hexane (90.7ml), and the mixture was stirred  
for 1 hour. To the mixture was added dropwise a solution  
of trimethyl borate (43.1g) in THF (43ml), and the mixture  
was stirred for 30 minutes and warmed to room temperature.  
To the mixture was added water (150ml), and the mixture was  
25 stirred for 15 minutes. The reaction mixture was extracted  
with ethyl acetate. Under reduced pressure, the solvent was  
evaporated, and the residue was stirred in methanol/water  
(2/1, 1000ml) for 3 days. Under reduced pressure, methanol  
was removed, and the residue was extracted with ethyl acetate,  
30 washed with saturated brine and dried with magnesium sulfate.  
Under reduced pressure, the solvent was evaporated, and the  
residue was washed with hexane/isopropylether to give  
4-(methoxymethoxy)phenyl borate (2.4g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.51 (3H, s), 5.26 (2H, s), 7.14 (2H,  
35 d, J=8.4Hz), 8.15 (2H, d, J=8.4Hz)

Working Example 87 (Production of Compound 86)



To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (500mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added  
5 4-(methoxymethoxy)phenyl borate (262mg) and potassium carbonate (292mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (56mg), and the  
10 mixture was stirred 100°C for 9 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography  
15 (ethyl acetate/ethanol =3/1) to give 7-(4-methoxymethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 86) (340mg).  
20 m.p. 227-229°C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.63-1.76 (4H, m), 2.21 (3H, s), 2.66 (1H, m), 3.12-3.20 (2H, m), 3.31-3.43 (2H, m), 3.51 (3H, s), 3.58 (2H, s), 3.68-3.76 (2H, m), 4.00-4.09 (2H, m), 5.24 (2H, s), 7.16 (2H, d, J=8.8Hz), 7.30-7.36 (2H, m), 7.51-7.68  
25 (7H, m), 8.01 (1H, s), 8.19 (1H, d, J=8.2Hz)  
IR(KBr) 3260, 2953, 1655, 1601, 1518, 1410, 1315, 1294, 1238, 1130, 997, 826cm<sup>-1</sup>

## Reference Example 105

In toluene (104ml) was dissolved 4-bromophenol (13g).  
30 To the mixture was added under ice-cooling 65% sodium hydride (6.0g), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added under ice-cooling 2-chloroethyl-N,N-dimethylammonium chloride (14.1g), and the mixture was refluxed for 2 hours and cooled  
35 to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate,

washed with 1N sodium hydroxide and saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=3/1) to give N-[2-(4-bromophenoxy)-N,N-dimethylamine (11.3g). In THF (100ml) was dissolved N-[2-(4-bromophenoxy)-N,N-dimethylamine (11.2g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (31.5ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (14.3g) in THF (10ml), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added water (56ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-[2-(dimethylamino)ethoxy]phenyl borate (1.5g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.43 (6H, s), 2.89 (2H, m), 4.20 (2H, m), 6.88 (2H, d, J=8.2Hz), 8.09 (2H, d, J=7.2Hz)

Working Example 88 (Production of Compound 87)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (500mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-[(2-dimethylamino)ethoxy]phenyl borate (321mg) and potassium carbonate (292mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (56mg), and the mixture was stirred at 100°C for 12 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography

(ethyl acetate/ethanol=3/1) and recrystallized from ethanol to give 7-[4-(2-dimethylamino)ethoxyphenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 87) (190mg).

5 m.p. 227-229°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.62-1.87 (4H, m), 2.21 (3H, s), 2.37 (6H, s), 2.65 (1H, m), 2.78 (2H, t, J=5.8Hz), 3.11-3.20 (2H, m), 3.32-3.44 (2H, m), 3.58 (2H, s), 3.68-3.76 (2H, m),

10 4.00-4.10 (2H, m), 4.13 (2H, t, J=5.8Hz), 7.04 (2H, d, J=8.8Hz), 7.30-7.35 (2H, m), 7.51-7.69 (7H, m), 7.96 (1H, s), 8.19 (1H, d, J=8.4Hz)

IR(KBr) 3245, 2946, 1655, 1607, 1520, 1412, 1318, 1294, 1254, 1130, 824cm<sup>-1</sup>

15 Reference Example 106

In 4-methyl-2-pentanone (96ml) was dissolved 4-bromophenol (12g). To the mixture were added at room temperature potassium carbonate (24g) and 4-[2-(chloroethyl)morpholine hydrochloride (16.9g), and the

20 mixture was refluxed for 18 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the

25 residue was filtrated to give 4-[2-(4-bromophenoxy)ethyl]morpholine (16.9g). In THF (100ml) was dissolved 4-[2-(4-bromophenoxy)ethyl]morpholine (16.5g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (31.5ml), and the mixture was stirred

30 for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (14.3g) in THF (10ml), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added water (56ml), and the mixture was

35 stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the

solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-[2-(4-morpholino)ethoxy]phenyl borate (1.5g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.38-2.62 (4H, m), 3.56-3.65 (6H, m), 4.10 (2H, t, J=6.2Hz), 6.93 (2H, d, J=9.2Hz), 7.24-7.32 (2H, m)

Working Example 89 (Production of Compound 88)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (500mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-[2-(4-morpholino)ethoxy]phenyl borate (386mg) and potassium carbonate (292mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (56mg), and the mixture was stirred at 100°C for 12 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-[2-(4-morpholino)ethoxy]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 88) (190mg). m.p. 203-206°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.63-1.84 (4H, m), 2.23 (3H, s), 2.60 (4H, t, J=4.8Hz), 2.71 (1H, m), 2.84 (2H, t, J=5.6Hz), 3.16-3.19 (2H, m), 3.29-3.41 (2H, m), 3.62 (2H, s), 3.66-3.77 (6H, m), 3.98-4.19 (2H, m), 4.17 (2H, t, J=5.6Hz), 7.01 (2H, d, J=8.8Hz), 7.32-7.41 (3H, m), 7.50-7.66 (7H, m), 8.14-8.19 (2H, m)

IR(KBr) 3293, 2951, 1667, 1607, 1518, 1408, 1292, 1250, 1130, 826cm<sup>-1</sup>

Anal. for C<sub>36</sub>H<sub>43</sub>N<sub>3</sub>O<sub>6</sub>S

Calcd. C, 66.95 ; H, 6.71 ; N, 6.51

Found. C, 66.08 ; H, 6.71; N, 6.54

Working Example 90 (Production of Compound 89)

- In THF/acetone (1/1, 60ml) was dissolved 7-(4-methoxymethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (650mg). To the mixture was added 1N sulfuric acid (4.4ml), and the mixture was stirred at 65°C for 14 hours, cooled to room temperature and neutralized with saturated sodium bicarbonate solution. Under reduced pressure, the solvent was evaporated, and the residue was added to water. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was recrystallized from ethanol to give 7-(4-hydroxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 89) (530mg).
- m.p. 232-234°C
- <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.49-1.75 (4H, m), 2.11 (3H, s), 2.59 (1H, m), 3.03-3.11 (2H, m), 3.20-3.33 (2H, m), 3.53 (2H, s), 3.73-3.83 (2H, m), 3.86-3.98 (2H, m), 6.90 (2H, d, J=8.4Hz), 7.27 (2H, d, J=8.4Hz), 7.52 (1H, s), 7.63-7.69 (4H, m), 7.82 (1H, d, J=10.4Hz), 8.05 (2H, d, J=8.0Hz), 10.17 (1H, s)
- IR(KBr) 3223, 1655, 1599, 1524, 1410, 1318, 1128, 826cm<sup>-1</sup>
- Working Example 91 (Production of Compound 90)

- In DMF (4.8ml) was dissolved 7-(4-hydroxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (320mg). To the mixture was added potassium carbonate (96mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added t-butyl bromoacetate (0.093ml), and the mixture was stirred at room temperature for 4 hours. The mixture

was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(t-butoxycarbonylmethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 90) (274mg).

m.p. 209-211°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.51 (9H, s), 1.64-2.05 (4H, m), 2.23 (3H, s), 2.66 (1H, m), 3.12-3.23 (2H, m), 3.27-3.44 (2H, m), 3.58 (2H, s), 3.65-3.76 (2H, m), 3.99-4.12 (2H, m), 4.58 (2H, s), 7.00 (2H, d, J=8.8Hz), 7.29 (1H, s), 7.35 (2H, d, J=8.8Hz), 7.50-7.68 (6H, m), 8.18 (1H, d, J=8.0Hz), 8.47 (1H, s)

IR(KBr) 3241, 2949, 1752, 1655, 1601, 1522, 1410, 1292, 1130, 831cm<sup>-1</sup>

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>7</sub>S Calcd. C, 66.22 ; H, 6.67 ; N, 4.41 : Found. C, 66.27 ; H, 6.59; N, 4.36

Working Example 92 (Production of Compound 91)

In methylene chloride (6.4ml) was dissolved 7-[4-(t-butoxycarbonylmethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (160mg). To the mixture was added trifluoroacetic acid (6.4ml), and the mixture was stirred at room temperature for 22 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in ethanol/water and neutralized with saturated sodium bicarbonate solution. To the mixture was added 1N hydrochloric acid, and the precipitates were filtered, washed with water and a little amount of ethanol and dried to give 2-[4-[[4-[[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]anilino]carbonyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-7-

yl]phenoxy]acetic acid·hydrochloride (Compound 91) (70mg).

m.p. 172-175°C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.67-2.12 (4H, m), 2.23 (4H, s),  
3.03-3.13 (2H, m), 3.20-3.55 (4H, m), 3.74-3.85 (2H, m),  
5 3.95-4.07 (2H, m), 4.77 (2H, s), 7.07 (2H, d, J=8.6Hz), 7.54  
(d, J=8.6Hz), 7.58 (1H, s), 7.73-7.92 (5H, m), 8.05-8.12  
(2H, m)

IR(KBr) 1671, 1593, 1518, 1414, 1289, 1128, 816cm<sup>-1</sup>

Reference Example 107

10 In THF (300ml) was dissolved 4-bromobenzonitrile  
(25.1g). To the mixture was added dropwise at -100°C 1.6M  
n-butyllithium/hexane (94.8ml), and the mixture was stirred  
for 10 minutes. To the mixture was added dropwise trimethyl  
borate (26.5g), and the mixture was allowed to warm to room  
15 temperature for 6 hours. To the mixture was added 15%  
hydrochloric acid (50ml), and the mixture was stirred for  
15 minutes. The reaction mixture was extracted with ethyl  
acetate, washed with water (twice), washed with saturated  
brine and dried with magnesium sulfate. Under reduced  
20 pressure, the solvent was evaporated, and the residue was  
washed with hexane/isopropylether to give 4-  
(cyanophenyl)borate (12.5g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 7.77 (2H, d, J=7.8Hz), 7.94 (2H, d,  
J=8.4Hz), 8.40 (2H, br)

25 Working Example 93 (Production of Compound 92)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (400mg) was added  
toluene/ethanol/water (20/5/2, 21.6ml) and then were added  
30 4-cyanophenyl borate (147mg) and potassium carbonate  
(147mg), and the mixture was stirred at room temperature  
for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (46mg), and the  
mixture was refluxed for 6 hours and cooled to room  
35 temperature. The reaction mixture was added to water, and  
the mixture was extracted with ethyl acetate, washed with

- saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(4-cyanophenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 92) (90mg).
- m.p. 233-236°C.
- 10 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.60-1.83 (4H, m), 2.21 (3H, s), 2.66 (1H, m), 3.15-3.22 (2H, m), 3.32-3.42 (2H, m), 3.58 (2H, s), 3.70-3.78 (2H, m), 7.30-7.37 (4H, m), 7.55 (2H, d, J=8.4Hz), 7.68-7.83 (5H, m), 7.95 (1H, s), 8.29 (1H, d, J=8.0Hz)
- 15 IR(KBr) 3245, 2951, 2228, 1665, 1597, 1526, 1408, 1314, 1294, 1132, 828, 733cm<sup>-1</sup>

## Reference Example 108

- In DMF (150ml) was dissolved 5-bromosalicylaldehyde (18.6g). To the mixture was added at room temperature potassium carbonate (16.6g) and then was added iodoethane (17.3ml), and the mixture was stirred at 90°C for 3 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 5-bromo-2-ethoxybenzaldehyde (17.2g).
- 20
- 25

- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.48 (3H, t, J=7.2Hz), 3.13-3.20 (2H, m), 4.14 (2H, q, J=7.0Hz), 6.87 (1H, d, J=8.8Hz), 7.60 (1H, d, J=8.8, 2.6Hz), 7.91 (1H, d, J=2.6Hz), 10.41 (1H, s)
- 30

## Reference Example 109

- In formic acid (85.5ml) was dissolved 5-bromo-2-ethoxybenzaldehyde (17.1g). To the mixture was added hydroxylamine hydrochloride (7.8g), and the mixture was refluxed for 7 hours and cooled to room temperature. Under
- 35



reduced pressure, the solvent was evaporated, and the residue was washed with water and dried to give 5-bromo-2-ethoxybenzonitrile (15.8g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.48 (3H, t, J=7.0Hz), 4.14 (2H, q, J=7.0Hz), 6.85 (1H, d, J=8.8Hz), 7.57-7.66 (2H, m)  
IR(KBr) 2984, 2230, 1591, 1489, 1393, 1314, 1284, 1134, 1038, 810cm<sup>-1</sup>

#### Reference Example 110

In THF (180ml) was dissolved 5-bromo-2-ethoxybenzonitrile (15.8g). To the mixture was added dropwise at -100°C 1.6M n-butyllithium/hexane (48ml), and the mixture was stirred for 30 minutes. To the mixture was added dropwise trimethyl borate (14.5g), and the mixture was stirred for 20 minutes and allowed to warm to room temperature for 5 hours. To the mixture was added 4N hydrochloric acid (50ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with water (twice), washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 3-cyano-4-ethoxyphenyl borate (6.0g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.38 (3H, t, J=7.0Hz), 4.22 (2H, q, J=7.0Hz), 7.20 (1H, d, J=9.2Hz), 8.00-8.05 (1H, m), 8.18 (1H, s)

#### Working Example 94 (Production of Compound 93)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (400mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 3-cyano-4-ethoxyphenyl borate (205mg) and potassium carbonate (251mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (48mg), and the mixture was refluxed for 18 hours and cooled to room

temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(4-cyano-3-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 93) (209mg).

m.p. 244-247°C.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.41 (3H, t, J=7.0Hz), 1.45-1.73 (4H, m), 2.10 (3H, s), 2.59 (1H, m), 3.05-3.12 (2H, m), 3.21-3.30 (2H, m), 3.52 (2H, s), 3.74-3.84 (2H, m), 3.84-3.94 (2H, m), 4.28 (2H, q, J=7.0Hz), 7.26 (2H, d, J=8.4Hz), 7.39 (2H, d, J=9.2Hz), 7.53 (1H, s), 7.67 (2H, d, J=8.4Hz), 7.92-7.97 (2H, m), 8.06-8.25 (3H, m)

#### Reference Example 111

In DMF (160ml) was dissolved 5-bromosalicylaldehyde (20g). To the mixture was added at room temperature potassium carbonate (17.9g) and then was added 1-bromopropane (10.8ml), and the mixture was stirred at 90°C for 3 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=6/1) to give 5-bromo-2-propoxybenzaldehyde (21.9g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.07 (3H, t, J=7.4Hz), 1.80-1.95 (2H, m), 4.03 (2H, t, J=6.4Hz), 6.88 (1H, d, J=9.0Hz), 7.60 (1H, dd, J=8.8, 2.6Hz), 7.91 (1H, d, J=2.6Hz), 10.43 (1H, s)

#### Reference Example 112

In formic acid (110ml) was dissolved 5-bromo-2-propoxybenzaldehyde (21.8g). To the mixture was added

hydroxylamine hydrochloride (9.4g), and the mixture was refluxed for 7 hours and cooled to room temperature. Under reduced pressure, the solvent was evaporated, and the residue was added to 1N potassium hydroxide. The mixture  
5 was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 5-bromo-2-propoxybenzonitrile (15.8g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.07 (3H, t, J=7.4Hz), 1.80-1.95 (2H, m), 4.02 (2H, t, J=6.4Hz), 6.85 (1H, d, J=8.8Hz), 7.57-7.65 (2H, m)

IR(KBr) 2969, 2230, 1591, 1489, 1391, 1285, 1132, 972, 812cm<sup>-1</sup>

15 Reference Example 113

In THF (180ml) was dissolved 5-bromo-2-propoxybenzonitrile (15.3g). To the mixture was added dropwise at -100°C 1.6M n-butyllithium/hexane (44ml) and then trimethyl borate (13.2g), and the mixture was stirred  
20 for 20minutes and allowed to warm to room temperature for 5 hours. To the mixture was added 4N hydrochloric acid (50ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine  
25 and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 3-cyano-4-propoxyphenyl borate (7.0g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.01 (3H, t, J=7.4Hz), 1.70-1.85 (2H, m), 4.11 (2H, t, J=6.4Hz), 7.21 (1H, d, J=9.2Hz), 8.01-8.06 (2H, m), 8.19 (2H, br)

Working Example 95 (Production of Compound 94)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (400mg) was added  
35 toluene/ethanol/water (10/1/1, 13.2ml) and then were added

3-cyano-4-propoxyphenyl borate (205mg) and potassium carbonate (234mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture were added palladium acetate (8.6mg) and tris(2-methylphenyl)phosphine (22.4mg), and the mixture was refluxed for 18 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(4-cyano-3-propoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 94) (243mg).

m.p. 201-203°C.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.11 (3H, t, J=7.4Hz), 1.65-1.78 (4H, m), 1.86-2.00 (2H, m), 2.21 (3H, s), 2.65 (1H, m), 3.14-3.22 (2H, m), 3.30-3.44 (2H, m), 3.57 (2H, s), 3.69-3.77 (2H, m), 4.00-4.10 (2H, m), 4.11 (2H, t, J=6.6Hz), 7.08 (1H, d, J=9.0Hz), 7.30-7.37 (3H, m), 7.53-7.63 (4H, m), 7.71-7.77 (2H, m), 8.03 (1H, s), 8.22 (1H, d, J=8.4Hz)

IR(KBr) 3301, 2944, 2228, 1667, 1607, 1510, 1408, 1314, 1291, 1128, 819, 735cm<sup>-1</sup>

Anal. for C<sub>34</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>S Calcd. C, 68.09 ; H, 6.22 ; N, 7.01 ; Found. C, 67.83 ; H, 6.20 ; N, 6.89

Working Example 96 (Production of Compound 95)

In DMF (1.6ml) was dissolved 7-(4-hydroxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (131mg). To the mixture was added potassium carbonate (41mg), and the mixture was stirred for 50 minutes. To the mixture was added iodoacetamide (50mg), and the mixture was stirred at room temperature for 20 hours. The reaction mixture was added

to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(4-carbamoylmethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 95) (52mg).

m.p. 240-243°C.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.45-1.78 (4H, m), 2.21 (3H, s), 2.60 (1H, m), 3.01-3.13 (2H, m), 3.21-3.35 (2H, m), 3.53 (2H, s), 3.74-3.80 (2H, m), 3.86-3.95 (2H, m), 4.51 (2H, m), 7.10 (2H, d, J=8.8Hz), 7.27 (2H, d, J=8.8Hz), 7.40-7.93 (8H, m), 8.05 (1H, s), 8.22 (1H, d, J=8.4Hz)  
IR(KBr) 3320, 2951, 1669, 1597, 1518, 1408, 1291, 1130, 816cm<sup>-1</sup>

#### Reference Example 114

In DMF (108ml) was dissolved morpholine (9.0g). To the mixture were added at room temperature triethylamine (24ml) and 4-bromobenzyl bromide (21.5g), and the mixture was stirred at 80°C for 16 hours and cooled to room temperature.

The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give 4-(4-bromobenzyl)morpholine (17.2g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.38-2.45 (4H, m), 3.44 (2H, s), 3.67-3.73 (4H, m), 7.21 (2H, d, J=8.4Hz), 7.44 (2H, d, J=8.4Hz)

#### Reference Example 115

In THF (174ml) was dissolved 4-(4-bromobenzyl)morpholine (19.3g). To the mixture was added

dropwise at -78°C 1.6M n-butyllithium/hexane (52ml), and the mixture was stirred for 30 minutes. To the mixture was added dropwise a solution of trimethyl borate (21.8g) in THF (22ml), and the mixture was stirred for 30 minutes and  
5 warmed to room temperature. To the mixture was added water (73ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the  
10 residue was washed with hexane/isopropylether to give 4-(4-morpholinomethyl)phenyl borate (5.7g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.36-2.59 (4H, m), 3.48-3.81 (6H, m), 7.25-7.44 (2H, m), 7.93-8.10 (2H, m)

Working Example 97 (Production of Compound 96)

15 To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (560mg) was added toluene/ethanol/water (10/1/1, 18ml) and then were added  
4-(4-morpholinomethyl)phenyl borate (285mg) and potassium  
20 carbonate (327mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (62.2mg), and the mixture was refluxed for 14 hours and cooled to room temperature. The mixture was added to water, and the  
25 mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from  
30 ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(4-morpholinomethyl)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 96) (377mg).  
m.p. 211-213°C  
35 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.65-1.82 (4H, m), 2.21 (3H, s), 2.45-2.51 (2H, m), 2.65 (1H, m), 3.13-3.21 (2H, m), 3.31-3.45

- (2H, m), 3.56 (2H, s), 3.58 (2H, s), 3.71-3.77 (2H, m), 3.98-4.10 (2H, m), 7.30-7.37 (3H, m), 7.43-7.59 (6H, m), 7.66-7.74 (2H, m), 7.91 (1H, s), 8.22 (1H, d, J=8.2Hz)  
 IR(KBr) 3254, 2948, 1667, 1597, 1514, 1408, 1314, 1294, 1130, 866, 735cm<sup>-1</sup>
- 5    Anal. for C<sub>35</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>S Calcd. C, 68.27 ; H, 6.71 ; N, 6.82 ; Found. C, 68.10 ; H, 6.74 ; N, 6.75  
 Reference Example 116
- To methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (5.0g) was added  
 10    toluene/ethanol/water (10/1/1,188ml) and then were added 4-(2-ethoxyethoxy)phenyl borate (4.1g) and potassium carbonate (4.6g), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added  
 15    tetrakis(triphenylphosphine)palladium (0.7g), and the mixture was refluxed for 14 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with  
 20    saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give methyl 7-[4-(2-ethoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (4.6g).  
 25    <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J=7.0Hz), 3.10-3.18 (2H, m), 3.58-3.87 (2H, m), 3.66 (2H, q, J=7.0Hz), 3.87 (3H, s), 4.16-4.22 (2H, m), 7.04 (2H, dd, J=6.6, 1.8Hz), 7.55 (2H, dd, J=6.6, 1.8Hz), 7.64-7.70 (2H, m), 7.91 (1H, s), 8.19 (1H, d, J=8.8Hz)  
 30    IR(KBr) 2920, 1709, 1604, 1518, 1294, 1252, 1130, 828, 752m<sup>-1</sup>  
 Anal. for C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>S Calcd. C, 63.44 ; H, 5.81 ; Found. C, 63.27 ; H, 5.74  
 Reference Example 117
- To methyl 7-[4-(2-ethoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (4.35g) were  
 35    added 1,2-dimethoxyethane (87ml) and 6N hydrochloric acid

(43.5ml), and the mixture was refluxed at 100°C for 16 hours and cooled to room temperature. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give 7-[4-(2-ethoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (3.7g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.44 (3H, t, J=7.0Hz), 2.91-3.04 (2H, m), 3.52 (2H, q, J=7.0Hz), 3.70-3.77 (4H, m), 4.13-4.19 (2H, m), 7.09 (2H, d, J=8.8Hz), 7.78 (2H, d, J=8.8Hz), 7.85-7.92 (2H, m), 8.03 (1H, s), 8.18 (1H, s)

IR(KBr) 2978, 1684, 1606, 1518, 1412, 1292, 1252, 1165, 1128, 829cm<sup>-1</sup>

Anal. for C<sub>21</sub>H<sub>22</sub>O<sub>6</sub>S Calcd. C, 62.67 ; H, 5.51 : Found. C, 62.75 ; H, 5.60

Working Example 98 (Production of Compound 84)

In THF (72ml) was dissolved 7-[4-(2-ethoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (3.6g). To the mixture were added under ice-cooling thionyl chloride (0.93ml) and DMF (three drops), and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was added dropwise to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (2.23g) and triethylamine (5.0ml) in THF (67ml), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=3/1) and recrystallized from ethanol to give 7-[4-(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 84) (2.4g).



m.p. 215-217°C

Anal. for  $C_{34}H_{40}N_2O_6S$  Calcd. C, 67.53 ; H, 6.67 ; N, 4.63 ;

Found. C, 67.24 ; H, 6.62 ; N, 4.34

Reference Example 118

- 5 In DMF (120ml) was dissolved 4-bromophenol (20g). To the mixture were added potassium carbonate (24g) and sodium iodide (19.1g) and then was added dropwise 2-chloroethylpropylether (19ml), and the mixture was stirred at 80°C for 16 hours and cooled to room temperature. The  
10 reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl  
15 acetate=10/1) to give 1-bromo-4-(2-propoxyethoxy)benzene (23.1g).

$^1H$ -NMR (200MHz,  $CDCl_3$ )  $\delta$  0.93 (3H, t,  $J=7.2Hz$ ), 1.55-1.71 (2H, m), 3.48 (2H, t,  $J=6.8Hz$ ), 3.74-3.79 (2H, m), 4.05-4.10 (2H, m), 6.77-6.83 (2H, m), 7.33-7.38 (2H, m)

- 20 Reference Example 119

To a solution of magnesium (2.17g) in THF (43ml) was added 1,2-dibromoethane (3 drops). While refluxing the mixture, a solution of 1-bromo-4-(2-propoxyethoxy)benzene (22g) in THF (176ml) was gradually added to the mixture.

- 25 The mixture was stirred for 15 minutes and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (13.2g) in THF (13ml), and the mixture was stirred for 1 hour, allowed to warm to room temperature for 6 hours and stirred at room temperature for 8 hours. To the mixture  
30 was added 5% sulfuric acid (75ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the  
35 residue was washed with hexane/isopropylether and then hexane/ethyl acetate to give 4-(2-propoxyethoxy)phenyl

borate (8.6g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.87 (3H, t, J=7.4Hz), 1.44-1.62 (2H, m), 3.41 (2H, t, J=6.6Hz), 3.67-3.72 (2H, m), 4.07-4.12 (2H, m), 6.89 (2H, d, J=8.8Hz), 7.73 (2H, d, J=8.8Hz)

5 Working Example 99 (Production of Compound 97)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (400mg) was added toluene/ethanol/water (10/1/1, 19.2ml) were added 4-(2-propoxyethoxy)phenyl borate (207mg) and potassium carbonate (234mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (36mg), and the mixture was refluxed for 8 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 97) (218mg).

25 m.p. 195-197°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.2Hz), 1.60-1.80 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13-3.20 (2H, m), 3.31-3.44 (2H, m), 3.52 (2H, t, J=6.8Hz), 3.57 (2H, s), 3.68-3.75 (2H, m), 3.82 (2H, t, J=4.8Hz), 4.10-4.20 (2H, m), 4.19 (2H, t, J=4.8Hz), 7.04 (2H, d, J=8.8Hz), 7.30-7.35 (3H, m), 7.51-7.68 (6H, m), 7.83 (1H, s), 8.19 (1H, d, J=8.0Hz)  
IR(KBr) 3270, 2942, 1665, 1607, 1518, 1311, 1292, 1252, 1130, 826, 667cm<sup>-1</sup>

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 :  
35 Found. C, 67.87 ; H, 6.98 ; N, 4.45

Reference Example 120

In DMF (150ml) was dissolved 4-bromophenol (25g). To the mixture was added potassium carbonate (30g) and then was added dropwise 2-bromoethanol (23.5g), and the mixture was stirred at 90°C for 6 hours and cooled to room temperature.

- 5 The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography  
10 (hexane/ethyl acetate=2/1) to give 2-(4-bromophenoxy)-1-ethanol (15.9g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 2.24 (1H, br), 3.91-3.91 (2H, m), 4.02-4.07 (2H, m), 6.77-6.83 (2H, m), 7.33-7.38 (2H, m)  
Reference Example 121

- 15 In DMF (150ml) was dissolved 2-(4-bromophenoxy)-1-ethanol (15.7g). To the mixture was added under ice-cooling 65% sodium hydride (4.3g), and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise iodobutane (17.3g), and the mixture was stirred  
20 for 2 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography  
25 (hexane/ethyl acetate=4/1) to give 1-bromo-4-(2-butoxyethoxy)benzene (12.6g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.4Hz), 1.27-1.65 (4H, m), 3.53 (2H, t, J=6.6Hz), 3.74-3.79 (2H, m), 4.05-4.11 (2H, m), 6.81 (2H, d, J=9.0Hz), 7.36 (2H, d, J=9.0Hz)

- 30 Reference Example 122

- To a solution of magnesium (1.14g) in THF (23ml) was added 1,2-dibromoethane (3 drops). While refluxing the mixture, a solution of 1-bromo-4-(2-butoxyethoxy)benzene (12.2g) in THF (98ml) was gradually added dropwise to the  
35 mixture. The mixture was stirred for 15 minutes and cooled to -78°C. To the mixture was added dropwise trimethyl borate

(6.9g), and the mixture was stirred for 1 hour, allowed to warm to room temperature for 8 hours and stirred at room temperature for 6 hours. To the mixture was added 5% sulfuric acid (75ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether and then hexane/ethyl acetate to give 4-(2-butoxyethoxy)phenyl borate (6.0g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.2Hz), 1.25-1.58 (2H, m), 3.45 (2H, t, J=6.6Hz), 3.64-3.76 (2H, m), 4.03-4.16 (2H, m), 6.87-6.96 (2H, m), 7.14 (1H, d, J=8.4Hz), 7.81 (1H, d, J=8.4Hz)

Working Example 100 (Production of Compound 98)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (400mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-(2-butoxyethoxy)phenyl borate (221mg) and potassium carbonate (234mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (36mg), and the mixture was refluxed for 8 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 98) (330mg).

m.p. 194-196°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.2Hz), 1.33-1.55 (2H, m), 1.57-1.77 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.16 (2H, t, J=6.4Hz), 3.31-3.44 (2H, m), 3.52-3.59 (2H, m), 3.57 (2H, s), 3.67-3.74 (2H, m), 3.79-3.84 (2H, m), 3.98-4.08 (2H, m), 4.18 (2H, t, J=4.8Hz), 7.03 (2H, d, J=8.8Hz), 7.30-7.35 (3H, m), 7.50-7.66 (6H, m), 7.88 (1H, s), 8.18 (1H, d, J=8.0Hz)

IR(KBr) 3300, 2935, 2853, 1667, 1607, 1518, 1312, 1292, 1251, 1130, 826cm<sup>-1</sup>

Anal. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 68.33 ; H, 7.01 ; N, 4.43 : Found. C, 68.33 ; H, 6.85 ; N, 4.39

#### Reference Example 123

In THF (100ml) was dissolved 3-ethoxypropanol (10g). To the mixture were added under ice-cooling triethylamine (14.5ml) and methanesulfonyl chloride (6.8ml), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added to water, and the mixture was extracted with THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was added dropwise under ice-cooling to a solution of 4-bromophenol (20.8g) and potassium carbonate (18.2g) in DMF (130ml). The mixture was stirred at 90°C for 60 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=10/1) to give 1-bromo-4-(3-ethoxypropoxy)benzene (10.8g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.20 (3H, t, J=7.0Hz), 1.98-2.08 (2H, m), 3.49 (2H, q, J=7.0Hz), 3.58 (2H, d, J=6.0Hz), 4.03 (2H, d, J=6.4Hz), 6.79 (2H, d, J=9.0Hz), 7.36 (2H, d, J=9.0Hz)

#### Reference Example 124

To a solution of magnesium (1.03g) in THF (21ml) was added 1,2-dibromoethane (3 drops). While refluxing the

mixture, a solution of 1-bromo-4-(3-ethoxypropoxy)benzene (10.5g) in THF (84ml) was gradually added dropwise to the mixture. The mixture was stirred for 15 minutes and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (6.3g) in THF (6ml), and the mixture was stirred for 1 hour, allowed to warm to room temperature for 6 hours and stirred at room temperature for 8 hours. To the mixture was added 5% sulfuric acid (42ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(3-ethoxypropoxy)phenyl borate (5.94g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.11 (3H, t, J=7.0Hz), 1.89-1.98 (2H, m), 3.42 (2H, q, J=7.0Hz), 3.50 (2H, t, J=6.2Hz), 4.02 (2H, t, J=6.2Hz), 6.84-6.93 (2H, m), 7.69-7.81 (2H, m)  
Working Example 101 (Production of Compound 99)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (400mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-(3-ethoxypropoxy)phenyl borate (207mg) and potassium carbonate (234mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (36mg), and the mixture was refluxed for 12 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(3-ethoxypropoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide

(Compound 99) (140mg).

m.p. 214-215°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.21 (3H, t, J=7.0Hz), 1.69-1.77 (4H, m), 2.05-2.13 (2H, m), 2.21 (3H, s), 2.65 (1H, m), 3.16 (2H, t, J=6.6Hz), 3.31-3.44 (2H, m), 3.51 (2H, q, J=7.0Hz), 3.57 (2H, s), 3.62 (2H, t, J=6.2Hz), 3.67-3.75 (2H, m), 3.98-4.16 (4H, m), 7.01 (2H, d, J=8.8Hz), 7.29-7.35 (3H, m), 7.50-7.67 (6H, m), 7.86 (1H, s), 8.18 (1H, d, J=8.0Hz)

IR(KBr) 3274, 2953, 1665, 1601, 1520, 1316, 1292, 1250, 1130, 824cm<sup>-1</sup>

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 : Found. C, 67.67 ; H, 6.77; N, 4.54

Reference Example 125

In DMF (120ml) was dissolved 4-bromobenzyl alcohol (10.1g). To the mixture was added under ice-cooling 65% sodium hydride (3.6g), and the mixture was stirred at room temperature for 3 hours. To the mixture was added dropwise at room temperature iodoethane (12.6g), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 1-bromo-4-(ethoxymethyl)benzene (10.1g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=7.0Hz), 2.53 (2H, q, J=7.0Hz), 4.45 (2H, s), 7.22 (2H, d, J=8.6Hz), 7.46 (2H, d, J=8.6Hz)

Reference Example 126

In THF/ether (4/1, 100ml) was dissolved 1-bromo-4-(ethoxymethyl)benzene (9.8g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (31.3ml), and the mixture was stirred for 1 hour. To the mixture was added trimethyl borate (11.8g), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture

was added 5% sulfuric acid (39ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(ethoxymethyl)phenyl borate (3.05g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.15 (3H, t, J=7.0Hz), 3.48 (2H, q, J=7.0Hz), 4.45 (2H, s), 7.27 (2H, d, J=8.0Hz), 7.76 (2H, d, J=8.0Hz)

Working Example 102 (Production of Compound 100)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-(ethoxymethyl)phenyl borate (125mg) and potassium carbonate (175mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (26.6mg), and the mixture was refluxed for 14 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(ethoxymethyl)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 100) (245mg).

m.p. 221-224°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.28 (3H, t, J=7.0Hz), 1.65-1.77 (4H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13-3.21 (2H, m), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.60 (2H, q, J=7.0Hz), 4.00-4.09 (2H, m), 4.57 (2H, s), 7.29-7.37 (3H, m), 7.44-7.68 (8H, m), 7.88 (1H, s), 8.19 (1H, d, J=8.0Hz)



IR(KBr) 3274, 2949, 1655, 1526, 1410, 1315, 1294, 1130, 814cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 68.96 ; H, 6.66 ; N, 4.87

5 Found. C, 68.72 ; H, 6.65 ; N, 4.86

Reference Example 127

In DMF (120ml) was dissolved 4-bromobenzyl alcohol (15g). To the mixture was added under ice-cooling 65% sodium hydride (3.0g), and the mixture was stirred at room temperature for 3 hours. To the mixture was added dropwise at room temperature 2-bromoethylethyl ether (11.4g), and the mixture was stirred at room temperature for 3 hours.

The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography

(hexane/ethyl acetate=10/1) to give 1-bromo-4-[(2-ethoxyethoxy)methyl]benzene (9.0g). In THF (104ml) was dissolved 1-bromo-4-[(2-ethoxyethoxy)methyl]benzene (8.7g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (23ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise trimethyl borate (8.7g), and the mixture was stirred for 30 minutes

25 and warmed to room temperature. To the mixture was added 5% sulfuric acid (35ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=1/2) to give

4-[(2-ethoxyethoxy)methyl]phenyl borate (2.1g).

30 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.25 (3H, t, J=7.0Hz), 3.57 (2H, q, J=7.0Hz), 3.58-3.67 (2H, m), 4.68 (2H, s), 7.50 (2H, d, J=8.0Hz), 8.22 (2H, d, J=8.0Hz)

35 Working Example 103 (Production of Compound 101)

- To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (400mg) was added toluene/ethanol/water (10/1/1, 25.5ml) and then were added
- 5 4-[(2-ethoxyethoxy)methyl]phenyl borate (260mg) and potassium carbonate (234mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (35.5mg), and the mixture was refluxed for 14 hours and cooled to room
- 10 temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from
- 15 ethanol to give 7-[4-[(2-ethoxyethoxy)methyl]phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 101) (282mg).
- 20 m.p. 184-186°C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=7.0Hz), 1.63-1.79 (4H, m), 2.20 (3H, s), 2.64 (1H, m), 3.12-3.20 (2H, m), 3.30-3.44 (2H, m), 3.50-3.61 (4H, m), 3.62-3.73 (2H, m), 3.66 (2H, s), 3.98-4.09 (2H, m), 4.64 (2H, s), 7.30-7.37 (3H, m),
- 25 7.45-7.72 (9H, m), 7.85 (1H, s), 8.22 (1H, d, J=8.0Hz)
- IR(KBr) 3300, 2926, 1667, 1597, 1526, 1408, 1313, 1294, 1130, 815cm<sup>-1</sup>
- Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 ; Found. C, 67.69 ; H, 6.90 ; N, 4.53
- 30 Reference Example 128

In DMF (150ml) was dissolved 4-bromophenol (25g). To the mixture was added potassium carbonate (30g) and then was added dropwise 3-bromopropanol (26.1g), and the mixture was stirred at 100°C for 20 hours and cooled to room

35 temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with

saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give 3-(4-bromophenoxy)-

5 1-propanol (20.6g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.76 (1H, br), 1.97-2.09 (2H, m), 3.80-3.91 (2H, m), 4.08 (2H, t, J=6.0Hz), 6.76-6.81 (2H, m), 7.33-7.40 (2H, m).

Reference Example 129

10 In DMF (100ml) was dissolved 3-(4-bromophenoxy)-1-propanol (10.0g). To the mixture was added under ice-cooling 65% sodium hydride (2.4g), and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise iodoethane (3.8ml), and the mixture was  
15 stirred for 3 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography  
20 (hexane/ethyl acetate=4/1) to give 1-bromo-4-(3-methoxypropoxy)benzene (8.6g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.4Hz), 1.27-1.65 (4H, m), 3.53 (2H, t, J=6.6Hz), 3.74-3.79 (2H, m), 4.05-4.11 (2H, m), 6.81 (2H, d, J=9.0Hz), 7.36 (2H, d, J=9.0Hz)

25 Reference Example 130.

To a solution of magnesium (0.89g) in THF (17.7ml) was added iodine (catalytic amount). While refluxing the mixture, a solution of 1-bromo-4-(3-methoxypropoxy)benzene (8.5g) in THF (68ml) was gradually added dropwise to the  
30 mixture. The mixture was stirred for 1 hour and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (5.4g) in THF (10.8ml), and the mixture was stirred for 1 hour, allowed to warm to room temperature for 6 hours, and stirred at room temperature for 8 hours.  
35 To the mixture was added 5% sulfuric acid (34ml), and the mixture was stirred for 15 minutes. The reaction mixture

was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with

- 5 hexane/isopropylether and then hexane/ethyl acetate to give 4-(3-methoxypropoxy)phenyl borate (4.0g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.2Hz), 1.25-1.58 (2H, m), 3.45 (2H, t, J=6.6Hz), 3.64-3.76 (2H, m), 4.03-4.16 (2H, m), 6.87-6.96 (2H, m), 7.14 (1H, d, J=8.4Hz), 7.81 (1H, d, J=8.4Hz)

10 Working Example 104 (Production of Compound 102)

- To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added
- 15 toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-(3-methoxypropoxy)phenyl borate (145mg) and potassium carbonate (175mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the
- 20 mixture was refluxed for 14 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the
- 25 residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(3-methoxypropoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 102) (190mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.63-1.82 (4H, m), 2.03-2.15 (2H, m), 2.20 (3H, s), 2.64 (1H, m), 3.11-3.19 (2H, m), 3.31-3.44 (2H, m), 3.37 (3H, s), 3.55 (2H, s), 3.53-3.58 (2H, m), 3.60-3.73 (2H, m), 4.01-4.13 (2H, m), 4.12 (2H, t, J=6.2Hz), 7.01 (2H, d, J=8.4Hz), 7.26-7.35 (3H, m), 7.48-7.64 (6H, m), 7.94 (1H, s), 8.16 (1H, d, J=8.0Hz)

IR(KBr) 3270, 2949, 1667, 1607, 1518, 1408, 1311, 1292, 1252, 1130, 826cm<sup>-1</sup>

Anal. for C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.53 ; H, 6.67 ; N, 4.63 :  
Found. C, 67.39 ; H, 6.38 ; N, 4.71

5 Reference Example 131

In DMF (100ml) was dissolved 3-(4-bromophenoxy)-1-propanol (10.0g). To the mixture was added under ice-cooling 65% sodium hydride (2.4g), and the mixture was stirred at room temperature for 2 hours. To the mixture was  
10 added dropwise bromopropane (5.5ml), and the mixture was stirred for 3 hours. To the mixture was added 65% sodium hydride (0.8g), and the mixture was stirred at 70°C for 1 hour and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl  
15 acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=5/1) to give 1-bromo-4-(3-propoxypropoxy)benzene (6.7g).  
20 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.4Hz), 1.27-1.65 (4H, m), 3.53 (2H, t, J=6.6Hz), 3.74-3.79 (2H, m), 4.05-4.11 (2H, m), 6.81 (2H, d, J=9.0Hz), 7.36 (2H, d, J=9.0Hz)  
Reference Example 132

To a solution of magnesium (0.63g) in THF (12.5ml) was  
25 added iodine (catalytic amount). While refluxing the mixture, a solution of 1-bromo-4-(3-propoxypropoxy)benzene (6.7g) in THF (53.6ml) was gradually added dropwise to the mixture. The mixture was stirred for 1 hour and cooled to -78°C. To the mixture was added dropwise a solution of  
30 trimethyl borate (3.8g) in THF (7.6ml), and the mixture was stirred for 1 hour, allowed to warm to room temperature for 6 hours and stirred at room temperature for 8 hours. To the mixture was added 5% sulfuric acid (27ml), and the mixture was stirred for 15 minutes. The reaction mixture was added  
35 to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(3-propoxypropoxy)phenyl borate (2.0g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.2Hz), 1.25-1.58 (2H, m), 3.45 (2H, t, J=6.6Hz), 3.64-3.76 (2H, m), 4.03-4.16 (2H, m), 6.87-6.96 (2H, m), 7.14 (1H, d, J=8.4Hz), 7.81 (1H, d, J=8.4Hz)

Working Example 105 (Production of Compound 103)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) were added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 4-(3-propoxypropoxy)phenyl borate (165mg) and potassium carbonate (175mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 14 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(3-propoxypropoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 103) (245mg).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.2Hz), 1.54-1.92 (6H, m), 2.04-2.13 (2H, m), 2.20 (3H, s), 2.64 (1H, m), 3.11-3.18 (2H, m), 3.31-3.43 (2H, m), 3.41 (2H, t, J=6.6Hz), 3.56 (2H, s), 3.58-3.72 (4H, m), 4.00-4.11 (2H, m), 4.13 (2H, t, J=6.2Hz), 7.01 (2H, d, J=8.8Hz), 7.26-7.35 (3H, m), 7.48-7.63 (6H, m), 7.98 (1H, s), 8.15 (1H, d, J=8.0Hz)  
IR(KBr) 3274, 2955, 1655, 1601, 1520, 1410, 1316, 1292, 1252, 1130, 822cm<sup>-1</sup>

Anal. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 68.33 ; H, 7.01 ; N, 4.43 :

Found. C, 68.34 ; H, 6.82 ; N, 4.48

Reference Example 133

To methyl 7-bromo-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylate (6.5g) was added  
5 toluene/ethanol/water (10/1/1, 188ml) and then were added  
4-(2-propoxyethoxy)phenyl borate (5.3g) and potassium  
carbonate (6.0g), and the mixture was stirred at room  
temperature for 30 minutes. To the mixture was added  
10 tetrakis(triphenylphosphine)palladium (0.9g), and the  
mixture was refluxed for 14 hours and cooled to room  
temperature. The mixture was added to water, and the  
mixture was extracted with ethyl acetate, washed with  
saturated brine and dried with magnesium sulfate. Under  
15 reduced pressure, the solvent was evaporated, and the  
residue was purified with silica gel column chromatography  
(hexane/ethyl acetate=3/2) to give methyl 7-[4-(2-  
propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxylate (6.5g).  
m.p. 105-107°C.

20 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.4Hz), 1.56-1.76 (2H,  
m), 3.11-3.17 (2H, m), 3.52 (2H, t, J=6.8Hz), 3.60-3.68 (2H,  
m), 3.80-3.85 (2H, m), 3.87 (3H, s), 4.16-4.21 (2H, m), 7.04  
(2H, d, J=8.4Hz), 7.53-7.58 (2H, m), 7.65-7.70 (2H, m), 7.91  
(1H, s), 8.20 (1H, d, J=8.8Hz)  
25 IR(KBr) 2920, 1709, 1604, 1518, 1294, 1252, 1130, 828, 752cm<sup>-1</sup>  
Anal. for C<sub>23</sub>H<sub>26</sub>O<sub>6</sub>S Calcd. C, 64.17 ; H, 6.09 ; Found. C, 64.20 ;  
H, 5.91

Reference Example 134

To methyl 7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-  
30 2,3-dihydro-1-benzothiepine-4-carboxylate (6.5g) were  
added 1,2-dimethoxyethane (130ml) and 6N hydrochloric acid  
(65ml), and the mixture was refluxed at 100°C for 18 hours,  
cooled to room temperature, extracted with ethyl acetate,  
washed with saturated brine and dried with magnesium sulfate.  
35 Under reduced pressure, the solvent was evaporated to give  
7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-

benzothiepine-4-carboxylic acid (5.0g).

m.p. 176-179°C.

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.4Hz), 1.44-1.62 (2H, m), 2.93-3.00 (2H, m), 3.43 (2H, t, J=6.6Hz), 3.70-3.81 (4H, m), 4.14-4.19 (2H, m), 7.08 (2H, d, J=8.8Hz), 7.78 (2H, d, J=8.8Hz), 7.86-7.90 (2H, m), 8.05 (2H, m)  
IR(KBr) 2978, 1684, 1606, 1518, 1412, 1292, 1252, 1165, 1128, 829cm<sup>-1</sup>

Anal. for C<sub>22</sub>H<sub>24</sub>O<sub>6</sub>S Calcd. C, 63.44 ; H, 5.81 : Found. C, 63.38 ; H, 5.66

Working Example 106 (Production of Compound 97)

In THF (98ml) was dissolved 7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (4.9g). To the mixture were added under ice-cooling thionyl chloride (1.3ml) and DMF (3 drops), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added dropwise a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (2.93g) and triethylamine (6.6ml) in THF (88ml), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=3/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 97) (2.9g).

m.p. 195-197°C

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 : Found. C, 67.84 ; H, 6.82 ; N, 4.59

Reference Example 135

In DMF (75ml) was dissolved 4-bromophenol (7.5g). To the mixture were added at room temperature potassium



carbonate (7.2g) and sodium iodide (6.5g) and then was added dropwise 2-chloro-5-chloromethylthiophene (6.5g), and the mixture was stirred at 90°C for 6 hours and cooled to room temperature. The reaction mixture was added to water, and  
5 the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=10/1) to give 4-bromophenyl (5-  
10 chloro-2-thienyl)methyl ether (8.2g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 5.07 (2H, s), 6.79-6.87 (4H, m), 7.34-7.42 (2H, m)

## Reference Example 136

In THF (97ml) was dissolved 4-bromophenyl(5-  
15 chloro-2-thienyl)methyl ether (8.1g). To the mixture was added at -78°C 1.6M n-butyllithium/hexane (8.3ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (5.5g) in THF (5.5ml), and the mixture was stirred for 30 minutes and warmed to  
20 room temperature. To the mixture was added 5% sulfuric acid (32ml), and the mixture was stirred for 15 minutes, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with  
25 hexane/isopropylether to give 4-[(5-chloro-2-thienyl)methoxy]phenyl borate (4.2g).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 5.24 (2H, s), 6.86 (2H, d, J=8.4Hz), 7.01-7.11 (2H, m), 7.74 (2H, d, J=8.4Hz)

## Working Example 107 (Production of Compound 104)

30 To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added  
4-[(5-chloro-2-thienyl)methoxy]phenyl borate (186mg) and  
35 potassium carbonate (175mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added

tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed at 100°C for 8 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =5/2) and recrystallized from ethanol to give 7-[4-[(5-chloro-2-thienyl)methoxy]phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 104) (137mg).

m.p. 207-210°C.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.60-1.82 (4H, m), 2.20 (3H, s), 2.65 (1H, m), 3.15 (2H, t, J=6.2Hz), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.65-3.73 (2H, m), 3.98-4.09 (2H, m), 5.17 (2H, s), 6.83 (1H, d, J=3.8Hz), 6.91 (1H, d, J=3.6Hz), 7.05 (2H, d, 8.8Hz), 7.29-7.54 (3H, m), 7.48-7.64 (6H, m), 7.98 (1H, s), 8.16 (1H, d, J=8.0Hz)

IR(KBr) 2949, 2845, 1663, 1607, 1514, 1454, 1408, 1292, 1242, 1157, 1130, 1009, 814cm<sup>-1</sup>

#### Reference Example 137

In DMF (96ml) was dissolved 4-bromobenzenethiol (12g). To the mixture were added dropwise at room temperature potassium carbonate (12.3g) and sodium iodide (10.5g) and then was added dropwise 2-chloroethylpropylether (9.6ml), and the mixture was stirred at 90°C for 14 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=10/1) to give 1-bromo-4-(2-propoxyethylthio)benzene (16.9g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.91 (3H, t, J=7.4Hz), 1.50-1.66 (2H,

m), 3.09 (2H, t, J=6.6Hz), 3.39 (2H, t, J=7.0Hz), 3.60 (2H, t, J=7.0Hz), 7.20-7.26 (2H, m), 7.37-7.42 (2H, m)

#### Reference Example 138

To a solution of magnesium (1.53g) in THF (23ml) was  
5 added iodine (catalytic amount). While refluxing the  
mixture, a solution of 1-bromo-4-(2-  
propoxyethylthio)benzene (16.5g) in THF (132ml) was  
gradually added dropwise to the mixture. The mixture was  
stirred for 30 minutes and cooled to -78°C. To the mixture  
10 was added dropwise a solution of trimethyl borate (9.3g)  
in THF (9.3ml), and the mixture was stirred for 1 hour,  
allowed to warm to room temperature for 8 hours and stirred  
at room temperature for 6 hours. To the mixture was added  
3N hydrochloric acid (66ml), and the mixture was stirred  
15 for 15 minutes. The reaction mixture was added to water,  
and the mixture was extracted with ethyl acetate, washed  
with saturated brine and dried with magnesium sulfate.  
Under reduced pressure, the solvent was evaporated, and the  
residue was washed with hexane/isopropylether to give  
20 4-(2-propoxyethylthio)phenyl borate (6.5g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.86 (3H, t, J=7.2Hz), 1.41-1.57  
(2H, m), 3.15 (2H, t, J=6.6Hz), 3.35 (2H, t, J=6.6Hz), 3.56  
(2H, t, J=6.6Hz), 7.27 (2H, d, J=8.0Hz), 7.71 (2H, d,  
J=8.0Hz), 7.99 (2H, br)

#### 25 Working Example 108 (Production of Compound 105)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (310mg) was added  
toluene/ethanol/water (10/1/1, 19.8ml) and then were added  
30 4-(2-propoxyethylthio)phenyl borate (172mg) and potassium  
carbonate (181mg), and the mixture was stirred at room  
temperature for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (28mg), and the  
mixture was refluxed at 100°C for 12 hours and cooled to room  
35 temperature. The mixture was added to water, and the  
mixture was extracted with ethyl acetate, washed with

- saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =5/2) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethylthio)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 105) (220mg). m.p. 198-200°C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J=7.4Hz), 1.54-1.82 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.13-3.22 (4H, m), 3.31-3.43 (2H, m), 3.47 (2H, t, J=7.0Hz), 3.57 (2H, s), 3.67 (2H, t, J=7.0Hz), 3.65-3.72 (2H, m), 4.01-4.09 (2H, m), 7.30-7.35 (2H, m), 7.42-7.57 (7H, m), 7.63-7.71 (2H, m), 7.87 (1H, s), 8.22 (1H, d, J=8.4Hz)
- IR(KBr) 2959, 2847, 1655, 1597, 1528, 1410, 1316, 1294, 1130, 816cm<sup>-1</sup>
- Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> Calcd. C, 66.22 ; H, 6.67 ; N, 4.41 ; Found. C, 66.03 ; H, 6.72 ; N, 4.41

Reference Example 139

- In DMF (166ml) was dissolved 2-(4-bromophenoxy)-1-ethanol (19.5g). To the mixture was added under ice-cooling 65% sodium hydride (5.3g), and the mixture was stirred at room temperature for 1.5 hours. To the mixture was added dropwise iodopentane (17.7ml), and the mixture was stirred for 2 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=10/1) to give 1-bromo-4-(2-pentyloxyethoxy)benzene (12.0g).
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.90 (3H, t, J=6.6Hz), 1.25-1.37 (4H, m), 1.57-1.68 (2H, m), 3.52 (2H, t, J=6.6Hz), 3.74-3.79 (2H, m), 4.05-4.11 (2H, m), 6.78-6.83 (2H, m), 7.33-7.39 (2H, m)

## Reference Example 140

To a solution of magnesium (0.91g) in THF (14ml) was added iodine (catalytic amount). While refluxing the mixture, a solution of 1-bromo-4-(2-

5 pentyloxyethoxy)benzene (11.8g) in THF (94ml) was gradually added dropwise to the mixture. The mixture was stirred for 30 minutes and cooled to -78°C. To the mixture was added dropwise trimethyl borate (5.7g), and the mixture was allowed to warm to room temperature for 8 hours and stirred  
10 at room temperature for 6 hours. To the mixture was added 5% sulfuric acid (47ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under  
15 reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether and then hexane/ethyl acetate to give 4-(2-pentyloxyethoxy)phenyl borate (5.6g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.86 (3H, t, J=6.6Hz), 1.22-1.59  
20 (6H, m), 3.44 (2H, t, J=6.6Hz), 3.66-3.71 (2H, m), 4.05-4.13 (2H, m), 6.88 (2H, d, J=8.6Hz), 7.72 (2H, d, J=8.6Hz), 7.82 (2H, br)

## Working Example 109 (Production of Compound 106)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (310mg) was added  
25 toluene/ethanol/water (10/1/1, 19.8ml) and then were added 4-(2-pentyloxyethoxy)phenyl borate (180mg) and potassium carbonate (181mg), and the mixture was stirred at room  
30 temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (28mg), and the mixture was refluxed for 8 hours and cooled to room temperature. The mixture was added to water, and the  
mixture was extracted with ethyl acetate, washed with  
35 saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the

residue was purified with silica gel column chromatography (ethyl acetate/ethanol =5/2) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-

- 5 pentyloxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 106) (188mg).  
m.p. 188-189°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.90 (3H, t, J=6.6Hz), 1.38-1.40 (4H, m), 1.56-1.77 (6H, m), 2.20 (3H, s), 2.64 (1H, m), 3.10-3.19  
10 (2H, m), 3.30-3.44 (2H, m), 3.55 (2H, t, J=6.6Hz), 3.56 (2H, s), 3.65-3.73 (2H, m), 3.79-3.85 (2H, m), 3.98-4.10 (2H, m), 4.15-4.21 (2H, m), 7.00-7.06 (2H, m), 7.29-7.34 (2H, m), 7.47-7.66 (7H, m), 7.95 (1H, s), 8.17 (1H, d, J=8.4Hz)  
IR(KBr) 2938, 2853, 1667, 1607, 1516, 1408, 1312, 1292,  
15 1251, 1130, 826cm<sup>-1</sup>

Anal. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 68.70 ; H, 7.17 ; N, 4.33 :  
Found. C, 68.64 ; H, 7.03 ; N, 4.31

#### Reference Example 141

- In DMF (195ml) was dissolved 2-(4-bromophenoxy)-1-  
20 ethanol (19.5g). To the mixture was added under ice-cooling 65% sodium hydride (5.3g), and the mixture was stirred at room temperature for 2 hours. To the mixture was added dropwise iodohexane (19.9ml), and the mixture was stirred for 2 hours. The reaction mixture was added to water, and  
25 the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 1-bromo-4-(2-  
30 hexyloxyethoxy)benzene (16.2g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.89 (3H, t, J=6.6Hz), 1.25-1.43 (6H, m), 3.52 (2H, t, J=6.6Hz), 3.74-3.79 (2H, m), 4.05-4.11 (2H, m), 6.78-6.84 (2H, m), 7.34-7.39 (2H, m)

#### Reference Example 142

- 35 To a solution of magnesium (1.19g) in THF (14ml) was added iodine (catalytic amount). While refluxing the

mixture, a solution of 1-bromo-4-(2-hexyloxyethoxy)benzene (16.0g) in THF (102ml) was gradually added dropwise to the mixture. The mixture was stirred for 15 minutes and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (7.2g) in THF (14ml), and the mixture was allowed to warm to room temperature for 8 hours and stirred at room temperature for 6 hours. To the mixture was added 5% sulfuric acid (64ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(2-hexyloxyethoxy)phenyl borate (6.7g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.86 (3H, t, J=6.6Hz), 1.18-1.59 (8H, m), 3.44 (2H, t, J=6.6Hz), 3.66-3.71 (2H, m), 4.04-4.12 (2H, m), 6.88 (2H, d, J=8.4Hz), 7.73 (2H, d, J=8.4Hz)

Working Example 110 (Production of Compound 107)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (310mg) was added toluene/ethanol/water (10/1/1, 19.8ml) and then were added 4-(2-hexyloxyethoxy)phenyl borate (190mg) and potassium carbonate (181mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (28mg), and the mixture was refluxed for 8 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =5/2) and recrystallized from ethanol to give 7-[4-(2-hexyloxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-

benzothiepine-4-carboxamide (Compound 107) (200mg).  
m.p. 180-182°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.89 (3H, t, J=7.2Hz), 1.21-1.46 (6H, m), 1.57-1.82 (6H, m), 2.21 (3H, s), 2.64 (1H, m), 3.16 (2H, t, J=6.6Hz), 3.31-3.43 (2H, m), 3.51-3.70 (2H, m), 3.57 (2H, s), 3.67-3.75 (2H, m), 3.98-4.09 (2H, m), 4.15-4.21 (2H, t, J=4.8Hz), 7.03 (2H, d, J=8.8Hz), 7.30-7.35 (3H, m), 7.50-7.66 (6H, m), 7.89 (1H, s), 8.18 (1H, d, J=8.4Hz)  
IR(KBr) 3245, 2953, 2855, 1651, 1605, 1518, 1412, 1316, 1294, 1252, 1130, 826cm<sup>-1</sup>

Working Example 111 (Production of Compound 108)

In DMF (3.8ml) was dissolved 7-(4-hydroxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (380mg). To the mixture was added potassium carbonate (252mg), and the mixture was stirred for 30 minutes. To the mixture was added 2-chloromethylpyridinehydrochloride (130mg), and the mixture was stirred at room temperature for 6 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate/THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[4-(2-pyridylmethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 108) (10mg).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.46-1.74 (4H, m), 2.10 (3H, s), 2.59 (1H, m), 3.02-3.14 (2H, m), 3.19-3.37 (2H, m), 3.52 (2H, s), 3.72-3.83 (2H, m), 3.88-3.94 (2H, m), 5.26 (2H, s), 6.90 (1H, d, J=8.4Hz), 7.16-7.39 (5H, m), 7.53-7.89 (8H, m), 8.40-8.09 (2H, m), 8.57-8.62 (1H, m), 10.17 (1H, s)

Reference Example 143

In DMF (100ml) was dissolved 3-bromophenol (10g). To



the mixture were added potassium carbonate (10.4g) and bromopropane (6.0ml), and the mixture was stirred at 60°C for 2 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=10/1) to give 1-bromo-3-propoxybenzene (11.2g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.03 (3H, t, J=7.2Hz), 1.72-1.86 (2H, m), 3.89 (2H, t, J=6.6Hz), 6.79-6.85 (1H, m), 7.03-7.17 (3H, m)

#### Reference Example 144

In THF (110ml) was dissolved 1-bromo-3-propoxybenzene (11.0g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (35.2ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (10.6g) in THF (10.6ml), and the mixture was stirred for 30 minutes and warmed to room temperature.

To the mixture was added 2N hydrochloric acid (44ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 3-propoxyphenyl borate (4.5g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.99 (3H, t, J=7.4Hz), 1.65-1.81 (2H, m), 3.91 (2H, t, J=6.6Hz), 6.90-6.95 (1H, m), 7.18 (3H, m), 7.99 (2H, br)

#### 30 Working Example 112 (Production of Compound 109)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-propoxyphenyl borate (125mg) and potassium carbonate (175mg), and the mixture was stirred at room temperature

for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 8 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 5/2) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(3-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 109) (282mg).

m.p. 219-221°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.07 (3H, t, J=7.2Hz), 1.63-1.90 (6H, m), 2.21 (3H, s), 2.64 (1H, m), 3.13-3.21 (2H, m), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.67-3.75 (2H, m), 3.95-4.09 (2H, m), 6.98 (1H, dd, J=8.2, 2.6Hz), 7.10-7.17 (2H, m), 7.29-7.43 (4H, m), 7.54 (2H, d, J=8.4Hz), 7.64-7.71 (2H, m), 7.88 (1H, s), 8.20 (1H, d, J=8.4Hz)  
IR(KBr) 3357, 2946, 2841, 1649, 1631, 1595, 1510, 1406, 1321, 1294, 1217, 1134, 785cm<sup>-1</sup>  
Anal. for C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>S Calcd. C, 68.96 ; H, 6.66 ; N, 4.87 ; Found. C, 68.77 ; H, 6.85 ; N, 4.88

Reference Example 145

In DMF (140ml) was dissolved 3-bromophenol (14g). To the mixture were added potassium carbonate (15.7g) and sodium iodide (12.1g) and then was added 2-chloroethylpropylether (12.3ml), and the mixture was stirred at 90°C for 18 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=12/1) to give 1-bromo-3-(2-propoxyethoxy)benzene (11.1g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.2Hz), 1.56-1.72 (2H, m), 3.49 (2H, t, J=6.6Hz), 3.74-3.80 (2H, m), 4.07-4.12 (2H, m), 6.81-6.89 (1H, m), 7.03-7.18 (3H, m)

Reference Example 146

5 To a solution of magnesium (0.99g) in THF (9.9ml) was added 1,2-dibromoethane (catalytic amount). To the mixture was gradually added dropwise at room temperature a solution of 1-bromo-3-(2-propoxyethoxy)benzene (10.5g) in THF (84ml). The mixture was stirred at 60°C for 1 hour and cooled  
10 to -78°C. To the mixture was added dropwise a solution of trimethyl borate (8.5g) in THF (17ml), and the mixture was allowed to warm to room temperature for 8 hours and stirred at room temperature for 12 hours. To the mixture was added 2N hydrochloric acid (42ml), and the mixture was stirred  
15 for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether and  
20 hexane/ethyl acetate to give 3-(2-propoxyethoxy)phenyl borate (3.5g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.2Hz), 1.46-1.63 (2H, m), 3.42 (2H, t, J=6.6Hz), 3.67-3.73 (2H, m), 4.05-4.10 (2H, m), 6.93-6.98 (2H, m), 7.19-7.37 (2H, m), 8.00 (2H, br)

Working Example 113 (Production of Compound 110)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added  
30 toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-(propoxyethoxy)phenyl borate (155mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the  
35 mixture was refluxed for 16 hours and cooled to room temperature. The mixture was added to water, and the

- mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =5/2) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[3-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 110) (154mg).
- m.p. 166-167°C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J=7.4Hz), 1.57-1.83 (6H, m), 2.21 (3H, s), 2.64 (1H, m), 3.18 (2H, t, J=6.6Hz), 3.31-3.45 (2H, m), 3.51 (2H, t, J=6.6Hz), 3.57 (2H, s), 3.68-3.75 (2H, m), 3.79-3.85 (2H, m), 4.01-4.16 (2H, m), 4.17-4.23 (2H, m), 6.97-7.03 (1H, m), 7.15-7.19 (2H, m), 7.30-7.44 (4H, m), 7.55 (2H, d, J=8.8Hz), 7.64-7.72 (2H, m), 7.84 (1H, s), 8.21 (1H, d, J=8.2Hz)
- IR(KBr) 2942, 2849, 1667, 1597, 1522, 1408, 1312, 1292, 1130cm<sup>-1</sup>
- Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 : Found. C, 67.78 ; H, 6.76 ; N, 4.50
- Reference Example 147
- In THF (150ml) was dissolved 2-isopropoxyethanol (15g). To the mixture were added under ice-cooling triethylamine (30.1ml) and methanesulfonyl chloride (14.6ml), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was added to water, and the mixture was extracted with THF, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was added dropwise under ice-cooling to a solution of 4-bromophenol (20.7g) and potassium carbonate (21.5g) in DMF (207ml), and the mixture was stirred at 70°C for 16 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under

reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=10/1) to give 1-bromo-4-(2-isopropoxyethoxy)benzene (16.4g).

- 5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.18 (3H, s), 1.21 (3H, s), 3.60-3.75 (1H, m), 4.04-4.09 (2H, m), 6.80 (2H, d, J=9.2Hz), 7.36 (2H, d, J=9.2Hz)

Reference Example 148

- 10 To a solution of magnesium (1.58g) in THF (24ml) was added 1,2-dibromoethane (catalytic amount). While refluxing the mixture, a solution of 1-bromo-4-(2-isopropoxyethoxy)benzene (10g) in THF (80ml) was gradually added dropwise to the mixture. The mixture was stirred at 50°C for 1 hour and cooled to -78°C. To the mixture was added
- 15 dropwise a solution of trimethyl borate (6.4g) in THF (9.6ml), and the mixture was stirred for 1 hour, allowed to warm to room temperature and stirred at room temperature for 8 hours.

- To the mixture was added 2N hydrochloric acid (40ml), and the mixture was stirred for 15 minutes. The reaction
- 20 mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 4-(2-

- 25 isopropoxyethoxy)phenyl borate (1.3g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.09 (3H, s), 1.12 (3H, s), 3.55-3.71 (3H, m), 4.03-4.09 (2H, m), 6.88 (2H, d, J=8.8Hz), 7.72 (2H, d, J=8.8Hz)

Working Example 114 (Production of Compound 111)

- 30 To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 4-(2-isopropoxyethoxy)phenyl borate (153mg) and potassium
- 35 carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added

- tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 12 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) and recrystallized from ethanol to give 7-[4-(2-isopropoxyethoxy)phenyl]-N-[4-  
5 [[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 111) (159mg).  
10 m.p. 214-215°C  
 $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.20 (3H, s), 1.23 (3H, s), 1.62-1.77 (4H, m), 2.21 (3H, s), 2.67 (1H, m), 3.16 (2H, t,  $J=6.6\text{Hz}$ ), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.64-3.74 (3H, m), 3.81 (2H, m), 4.00-4.18 (2H, m), 4.17 (2H, t,  $J=4.8\text{Hz}$ ), 7.03 (2H, d,  $J=8.8\text{Hz}$ ), 7.30-7.34 (3H, m), 7.50-7.67 (6H, m), 7.86 (1H, s), 8.18 (1H, d,  $J=8.2\text{Hz}$ )  
15 IR(KBr) 3274, 2953, 1665, 1601, 1520, 1316, 1292, 1250, 1130, 824 $\text{cm}^{-1}$   
Anal. for  $\text{C}_{35}\text{H}_{42}\text{N}_2\text{O}_6\text{S}$  Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 ; Found. C, 67.67 ; H, 6.77; N, 4.54  
Working Example 115 (Production of Compound 112)  
25 In THF (850ml) was dissolved N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (17.3g), and to the mixture was added at room temperature 4N hydrochloric acid/ethyl acetate  
30 (14ml). The mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was washed with ethyl acetate/acetone and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-  
35 1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide hydrochloride (Compound 112) (11.2g).

m.p. 213-215°C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.4Hz), 1.05-1.63 (2H, m), 1.70-2.21 (4H, m), 2.58 (3H, s), 2.50-2.60 (2H, m), 3.05-3.12 (2H, m), 3.23-3.49 (4H, m), 3.43 (2H, t, J=6.6Hz), 3.72-3.82 (2H, m), 3.94-4.03 (2H, m), 4.17 (2H, s), 4.38-4.49 (2H, m), 7.10 (2H, d, J=8.8Hz), 7.58-7.62 (2H, m), 7.76 (2H, d, J=8.8Hz), 7.83-7.90 (4H, m), 8.07 (2H, d, J=8.2Hz), 10.47 (1H, s), 10.62 (1H, br).

IR(KBr) 2961, 2870, 1667, 1597, 1520, 1412, 1321, 1292, 1248, 1132, 828cm<sup>-1</sup>

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S · HCl Calcd. C, 64.16 ; H, 6.61 ; N, 4.28 : Found. C, 63.97 ; H, 6.55 ; N, 4.18

#### Reference Example 149

In DMF (120ml) was dissolved 2-bromophenol (12g). To the mixture was added potassium carbonate (12.5g) and then was added bromopropane (7.2ml), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=12/1) to give 1-bromo-2-propoxybenzene (10.5g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.08 (3H, t, J=7.4Hz), 1.78-1.94 (2H, m), 3.98 (2H, t, J=6.6Hz), 6.77-6.91 (2H, m), 7.19-7.29 (1H, m), 7.19-7.29 (1H, dd, J=7.6, 1.8Hz)

#### Reference Example 150

In THF (101ml) was dissolved 1-bromo-2-propoxybenzene (10.1g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (32.3ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (9.8g) in THF (9.8ml), and the mixture was stirred for 30 minutes and warmed to room temperature.

To the mixture was added 2N hydrochloric acid (40ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with

saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 2-propoxyphenyl borate (5.3g).

- 5 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.00 (3H, t, J=7.2Hz), 1.70-1.83 (2H, m), 4.00 (2H, t, J=6.6Hz), 6.89-7.00 (2H, m), 7.33-7.42 (1H, m), 7.60 (2H, dd, J=7.2, 2.0Hz), 7.68 (2H, s)

Working Example 116 (Production of Compound 113)

- To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.8ml) and then were added 2-propoxyphenyl borate (125mg) and potassium carbonate (175mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed at 100°C for 8 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(2-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 113) (46mg).

m.p. 190-192°C

- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.97 (3H, t, J=7.2Hz), 1.62-1.81 (4H, m), 2.20 (3H, s), 2.64 (1H, m), 3.18 (2H, t, J=7.0Hz), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.69-3.76 (2H, m), 3.96 (2H, t, J=7.0Hz), 3.99-4.09 (2H, m), 6.97-7.09 (2H, m), 7.30-7.42 (5H, m), 7.51-7.56 (2H, m), 7.60-7.75 (2H, m), 7.81 (1H, s), 8.21 (1H, d, J=8.0Hz)
- 35 IR(KBr) 2938, 2920, 1667, 1599, 1529, 15166, 1408, 1312, 1294, 1130, 754cm<sup>-1</sup>



Anal. for  $C_{36}H_{44}N_2O_6S$  Calcd. C, 68.70 ; H, 7.17 ; N, 4.33 :  
Found. C, 68.64 ; H, 7.03 ; N, 4.31

Reference Example 151

In DMF (120ml) was dissolved 2-bromophenol (12g), and  
5 to the solution were added potassium carbonate (14.4g) and  
sodium iodide (10.4g). To the mixture was added 2-  
bromoethylpropylether (10.4ml), and the mixture was stirred  
at 90°C for 16 hours. The reaction mixture was added to water,  
and the mixture was extracted with ethyl acetate, washed  
10 with saturated brine and dried with magnesium sulfate.  
Under reduced pressure, the solvent was evaporated, and the  
residue was purified with silica gel column chromatography  
(hexane/ethyl acetate=12/1) to give 1-bromo-2-(2-  
propoxyethoxy)benzene (14.4g).  
15 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J=7.4Hz), 1.56-1.73 (2H,  
m), 3.55 (2H, t, J=6.6Hz), 3.82-3.87 (2H, m), 4.15-4.21 (2H,  
m), 6.79-6.96 (2H, m), 7.20-7.29 (1H, m), 7.53 (1H, dd,  
J=7.6, 1.6Hz)

Reference Example 152

20 To a solution of magnesium (1.39g) in THF (14ml) was  
added 1,2-dibromoethane (catalytic amount) and at room  
temperature a solution of 1-bromo-2-(2-  
propoxyethoxy)benzene (14.1g) in THF (113ml) was gradually  
added dropwise to the mixture. The mixture was stirred at  
25 60°C for 1 hour and cooled to -78°C. To the mixture was added  
dropwise a solution of trimethyl borate (8.5g) in THF (8.5ml),  
and the mixture was gradually warmed to room temperature  
and stirred at room temperature for 12 hours. To the mixture  
was added 2N hydrochloric acid (56ml), and the mixture was  
30 stirred for 15 minutes. The reaction mixture was added to  
water, and the mixture was extracted with ethyl acetate,  
washed with saturated brine and dried with magnesium sulfate.  
Under reduced pressure, the solvent was evaporated, and the  
residue was washed with hexane/isopropylether to give  
35 2-(2-propoxyethoxy)phenyl borate (12.2g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.89 (3H, t, J=7.2Hz), 1.50-1.62

(2H, m), 3.43 (2H, t, J=6.6Hz), 3.71-3.76 (2H, m), 4.15-4.20 (2H, m), 6.92-7.04 (2H, m), 7.35-7.44 (1H, m), 7.63-7.70 (3H, m)

Working Example 117 (Production of Compound 114)

5 To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added  
toluene/ethanol/water (20/1/1, 13.9ml) and then were added  
2-(propoxyethoxy)phenyl borate (155mg) and potassium  
10 carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 12 hours and cooled to room temperature. The mixture was added to water, and the  
15 mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from  
20 ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[2-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 114) (230mg).

m.p. 164-166°C

25 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.85 (3H, t, J=7.4Hz), 1.50-1.82 (6H, m), 2.20 (3H, s), 2.64 (1H, m), 3.19 (2H, t, J=6.2Hz), 3.32-3.42 (2H, m), 3.40 (2H, t, J=6.6Hz), 3.57 (2H, s), 3.69-3.78 (4H, m), 4.00-4.19 (2H, m), 4.16 (2H, t, J=6.6Hz), 7.02 (1H, d, J=8.4Hz), 7.09 (1H, d, J=8.2Hz), 7.29-7.34 (6H, m), 7.53 (2H, d, J=8.4Hz), 7.74-7.80 (2H, m), 8.18 (1H, d, J=8.2Hz)

30 IR(KBr) 2938, 2847, 1667, 1599, 1516, 1408, 1312, 1294, 1130, 754cm<sup>-1</sup>

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 ;

35 Found. C, 67.90 ; H, 6.89 ; N, 4.46

Reference Example 153

In DMF (120ml) was dissolved 3-bromophenol (12g). To the mixture was added potassium carbonate (12.5g) and then was added 2-bromoethylethyl ether (9.1ml), and the mixture was stirred at 70°C for 16 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=12/1) to give 1-bromo-3-(2-ethoxyethoxy)benzene (12.1g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=6.8Hz), 3.60 (2H, q, J=6.8Hz), 3.75-3.80 (2H, m), 4.07-4.12 (2H, m), 6.83-6.89 (1H, m), 7.05-7.14 (2H, m)

## Reference Example 154

To a solution of magnesium (1.25g) in THF (12.5ml) was added 1,2-dibromoethane (catalytic amount), and at room temperature a solution of 1-bromo-3-(2-ethoxyethoxy)benzene (12g) in THF (96ml) was gradually added dropwise to the mixture. The mixture was stirred at 60°C for 1 hour and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (7.6g) in THF (7.6ml), and the mixture was gradually warmed to room temperature and stirred at room temperature for 12 hours. To the mixture was added 2N hydrochloric acid (48ml), and the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 3-(2-ethoxyethoxy)phenyl borate (7.4g).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.24 (3H, t, J=6.8Hz), 3.51 (2H, t, J=6.8Hz), 3.67-3.72 (2H, m), 4.04-4.10 (2H, m), 6.92-6.98 (1H, m), 7.19-7.28 (1H, m), 7.33-7.37 (2H, m), 8.00 (2H, br)

## 35 Working Example 118 (Production of Compound 115)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-

yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-(2-ethoxyethoxy)phenyl borate (145mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 10 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-[3-(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 115) (152mg).

m.p. 180-182°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J=7.0Hz), 1.58-1.82 (4H, m), 2.21 (3H, s), 2.65 (1H, m), 3.17 (2H, t, J=6.6Hz), 3.31-3.44 (2H, m), 3.57 (2H, s), 3.61 (2H, q, J=7.0Hz), 3.71-3.75 (2H, m), 3.83 (2H, t, J=4.8Hz), 3.98-4.10 (2H, m), 4.20 (2H, t, J=4.8Hz), 6.97-7.03 (1H, m), 7.14-7.19 (2H, m), 7.30-7.44 (5H, m), 7.55 (2H, d, J=8.4Hz), 7.64-7.71 (2H, m), 7.95 (1H, s), 8.21 (1H, d, J=8.4Hz)  
IR(KBr) 2945, 2845, 1667, 1595, 1526, 1408, 1312, 1221, 1130cm<sup>-1</sup>

Working Example 119 (Production of Compound 116)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-chlorophenyl borate (108mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added

tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 10 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with  
5 saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(3-chlorophenyl)-N-[4-[[N-methyl-N-  
10 (tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 116) (64mg).

m.p. 221-224°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.58-1.81 (4H, m), 2.21 (3H, s), 2.65  
15 (1H, m), 3.15-3.22 (2H, m), 3.30-3.45 (2H, m), 3.57 (2H, s), 3.69-3.77 (2H, m), 4.00-4.10 (2H, m), 7.30-7.71 (11H, m), 7.82 (1H, s), 8.25 (1H, d, J=8.0Hz)  
IR(KBr) 2951, 2845, 1653, 1595, 1410, 1315, 1294, 1221, 1130cm<sup>-1</sup>

20 Reference Example 155

In DMF (96ml) was dissolved 3-bromophenol (12g). To the mixture was added potassium carbonate (12.5g) and then 2-bromoethylethyl ether (6.7ml), and the mixture was stirred at room temperature for 16 hours. The reaction mixture was  
25 added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=12/1) to give  
30 1-bromo-3-ethoxybenzene (11.6g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.40 (3H, t, J=7.0Hz), 4.00 (2H, q, J=7.0Hz), 6.78-6.84 (1H, m), 7.02-7.16 (3H, m)

Reference Example 156

In THF (115ml) was dissolved 1-bromo-3-ethoxybenzene  
35 (11.5g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (39.3ml), and the mixture was stirred

for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (11.9g) in THF (11.9ml), and the mixture was stirred for 30 minutes and warmed to room temperature.

To the mixture was added 2N hydrochloric acid (46ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 3-ethoxyphenyl borate (7.1g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.33 (3H, t, J=7.0Hz), 4.01 (2H, q, J=7.0Hz), 6.90-6.96 (1H, m), 7.18-7.47 (3H, m), 7.74 (2H, br)

Working Example 120 (Production of Compound 117)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-ethoxyphenyl borate (115mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 10 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(3-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 117) (180mg).

m.p. 192-195°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.45 (3H, t, J=7.0Hz), 1.66-1.79 (4H, m), 2.21 (3H, s), 2.64 (1H, m), 3.18 (2H, t, J=6.6Hz),

- 3.30-3.44 (2H, m), 3.57 (2H, s), 3.69-3.76 (2H, m), 3.99-4.10 (2H, m), 4.11 (2H, q, J=7.0Hz), 6.94-7.00 (1H, m), 7.10-7.19 (1H, m), 7.30-7.44 (4H, m), 7.54 (2H, d, J=8.4Hz), 7.65-7.73 (2H, m), 7.83 (1H, s), 8.22 (1H, d, J=8.4Hz)
- 5 IR(KBr) 2945, 1669, 1597, 1526, 1408, 1312, 1223, 1130cm<sup>-1</sup>
- Reference Example 157

- In DMF (120ml) was dissolved 2-bromophenol (12g). To the mixture was added potassium carbonate (12.5g) and then was added 2-bromoethylethyl ether (9.1ml), and the mixture
- 10 was stirred at 70°C for 4 hours. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel
- 15 column chromatography (hexane/ethyl acetate=12/1) to give 1-bromo-2-(2-ethoxyethoxy)benzene (14.8g).
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=7.0Hz), 3.66 (2H, q, J=7.0Hz), 3.82-3.88 (2H, m), 4.15-4.20 (2H, m), 6.79-6.95 (1H, m), 7.20-7.29 (1H, m), 7.53 (1H, dd, J=7.8, 1.4Hz)

- 20 Reference Example 158

- To a solution of magnesium (1.46g) in THF (14.6ml) was added 1,2-dibromoethane (catalytic amount), and at room temperature a solution of 1-bromo-2-(2-
- 25 ethoxyethoxy)benzene (14g) in THF (112ml) was gradually added dropwise to the mixture. The mixture was stirred at 60°C for 1 hour and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (8.9g) in THF (8.9ml), and the mixture was gradually warmed to room temperature.
- To the mixture was added 2N hydrochloric acid (56ml), and
- 30 the mixture was stirred for 15 minutes. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with
- 35 hexane/isopropylether to give 2-(2-ethoxyethoxy)phenyl borate (6.3g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.15 (3H, t, J=7.0Hz), 3.53 (2H, q, J=7.0Hz), 3.70-3.76 (2H, m), 4.14-4.20 (2H, m), 6.93-7.04 (2H, m), 7.35-7.44 (1H, m), 7.62-7.70 (3H, m)

Working Example 121 (Production of Compound 118)

- 5 To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added  
toluene/ethanol/water (20/1/1, 13.9ml) and then were added  
2-(2-ethoxyethoxy)phenyl borate (145mg) and potassium  
10 carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 10 hours and cooled to room temperature. The mixture was added to water, and the  
15 mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from  
20 ethanol to give 7-[2-(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 118) (245mg).

- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.16 (3H, t, J=7.0Hz), 1.63-1.78 (4H,  
25 m), 2.20 (3H, s), 2.64 (1H, m), 3.18 (2H, t, J=6.6Hz), 3.30-3.43 (2H, m), 3.51 (2H, q, J=7.0Hz), 3.56 (2H, s), 3.68-3.75 (2H, m), 3.98-4.07 (2H, m), 4.13-4.19 (2H, m), 6.99-7.11 (2H, m), 7.28-7.42 (5H, m), 7.52 (2H, d, J=8.4Hz), 7.74-7.79 (2H, m), 7.86 (1H, s), 8.17 (1H, d, J=8.8Hz)  
30 IR(KBr) 3347, 2944, 2845, 1642, 1597, 1510, 1410, 1290, 1132, 747cm<sup>-1</sup>

Reference Example 159

- In DMF (120ml) was dissolved 2-bromophenol (12g). To the mixture was added potassium carbonate (12.5g) and then  
35 was added iodoethane (6.7ml), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was



added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel  
5 column chromatography (hexane/ethyl acetate=12/1) to give 1-bromo-2-ethoxybenzene (12.2g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.47 (3H, t, J=7.0Hz), 4.10 (2H, q, J=7.0Hz), 6.76-6.90 (2H, m), 7.19-7.29 (1H, m), 7.50-7.56 (1H, m)

10 Reference Example 160

In THF (120ml) was dissolved 1-bromo-2-ethoxybenzene (12.0g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (41.0ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution  
15 of trimethyl borate (12.4g) in THF (12.4ml), and the mixture was stirred for 30 minutes and warmed to room temperature.

To the mixture was added 2N hydrochloric acid (48ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with  
20 saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 2-ethoxyphenyl borate (7.1g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.37 (3H, t, J=7.0Hz), 4.09 (2H, q, J=7.0Hz), 6.89-6.99 (1H, m), 7.33-7.42 (1H, dd, J=7.2, 1.6Hz), 7.66 (2H, s)

Working Example 122 (Production of Compound 119)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
30 benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 2-ethoxyphenyl borate (115mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added  
35 tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 14 hours and cooled to room

temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =3/1) and recrystallized from ethanol to give 7-(2-ethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 119) (145mg).

m.p. 171-173°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.36 (3H, t, J=7.0Hz), 1.63-1.77 (4H, m), 2.20 (3H, s), 2.64 (1H, m), 3.18 (2H, t, J=6.6Hz), 3.30-3.44 (2H, m), 3.57 (2H, s), 3.68-3.76 (2H, m), 4.00-4.10 (2H, m), 4.08 (2H, q, J=7.0Hz), 6.98-7.09 (2H, m), 7.30-7.52 (5H, m), 7.54 (2H, d, J=8.4Hz), 7.66 (1H, s), 7.72 (1H, dd, J=8.0, 1.4Hz), 7.88 (1H, s), 8.18 (1H, d, J=8.0Hz)  
IR(KBr) 3270, 2944, 1645, 1599, 1514, 1410, 1319, 1292, 1130, 748cm<sup>-1</sup>

#### 20 Reference Example 161

In THF (150ml) was dissolved 1-bromo-3-trifluoromethylbenzene (15.0g). To the mixture was added dropwise at -78°C 1.6M n-butyllithium/hexane (45.8ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of trimethyl borate (13.9g) in THF (13.9ml), and the mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 2N hydrochloric acid (60ml), and the mixture was stirred for 15 minutes. The reaction mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 3-trifluoromethylphenyl borate (5.7g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 7.53-7.80 (3H, m), 8.06-8.21 (1H, m), 8.13 (2H, s)

## Working Example 123 (Production of Compound 120)

- To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added
- 5 toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-trifluoromethylphenyl borate (131mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added
- 10 tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 10 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under
- 15 reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =4/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-7-(3-trifluoromethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide
- 20 (Compound 120) (148mg).  
m.p. 236-238°C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.62-1.81 (4H, m), 2.20 (3H, s), 2.65 (1H, m), 3.19 (2H, t, J=6.6Hz), 3.31-3.43 (2H, m), 3.57 (2H, s), 3.70-3.78 (2H, m), 3.98-4.10 (2H, m), 7.30-7.38 (3H, m), 7.52-7.87 (9H, m), 8.27 (1H, d, J=8.0Hz)
- 25 IR(KBr) 2942, 1648, 1599, 1530, 1412, 1318, 1294, 1130, 801cm<sup>-1</sup>  
Anal. for C<sub>31</sub>H<sub>31</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>S Calcd. C, 63.68 ; H, 5.34 ; N, 4.79 ;  
Found. C, 63.51 ; H, 5.42 ; N, 4.70
- 30 Reference Example 162  
In DMF (120ml) was dissolved 4-bromo-3-methylphenol (12g). To the mixture were added potassium carbonate (11.5g) and sodium iodide (9.6g) and then added dropwise 2-chloroethylpropylether (9.7ml), and the mixture was
- 35 stirred at 90°C for 10 hours and cooled to room temperature.  
The reaction mixture was added to water, and the mixture

was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography

5 (hexane/ethyl acetate=12/1) to give 4-bromo-3-methyl-1-(2-propoxyethoxy)benzene (11.0g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.2Hz), 1.54-1.71 (2H, m), 2.25 (3H, s), 3.48 (2H, t, J=6.6Hz), 3.73-3.79 (2H, m), 4.05-4.10 (2H, m), 6.63 (1H, dd, J=8.8, 2.8Hz), 6.82 (1H, d, J=2.8Hz), 7.38 (1H, d, J=8.8Hz)

10 Reference Example 163

To a solution of magnesium (0.98g) in THF (9.8ml) was added 1,2-dibromoethane (3 drops). While refluxing the mixture, a solution of 4-bromo-3-methyl-1-(2-propoxyethoxy)benzene (10.5g) in THF (84ml) was gradually added dropwise to the mixture. The mixture was stirred for 15 minutes and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (6.0g) in THF (6.0ml), and the mixture was gradually warmed to room temperature and stirred at room temperature for 6 hours. To the mixture was added 2N hydrochloric acid (42ml), and the mixture was stirred for 15 minutes, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 2,3-dimethyl-4-(2-propoxyethoxy)phenyl borate (3.8g).

25 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J=7.2Hz), 1.42-1.61 (2H, m), 2.63 (3H, s), 3.41 (2H, t, J=6.6Hz), 3.66-3.72 (2H, m), 4.03-4.10 (2H, m), 6.65-6.74 (2H, m), 7.82 (1H, d, J=9.2Hz)

30 Working Example 124 (Production of Compound 121)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 2-methyl-4-(2-propoxyethoxy)phenyl borate (165mg) and

potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 14 hours and cooled to room temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =4/1) and recrystallized from ethanol to give 7-[2-methyl-4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 121) (184mg).  
m.p. 149-151°C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J=7.4Hz), 1.56-1.82 (6H, m), 2.20 (3H, s), 2.64 (1H, m), 3.18 (2H, t, J=6.4Hz), 3.30-3.43 (2H, m), 3.51 (2H, t, J=6.4Hz), 3.56 (2H, s), 3.68-3.75 (2H, m), 3.78-3.83 (2H, m), 3.99-4.18 (2H, m), 6.79-6.87 (2H, m), 7.11 (1H, d, J=8.2Hz), 7.28-7.55 (7H, m), 7.91 (1H, s), 8.18 (1H, d, J=8.2Hz)  
IR(KBr) 3374, 2953, 1659, 1609, 1505, 1406, 1290, 1242, 1127cm<sup>-1</sup>  
Anal. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 68.33 ; H, 7.01 ; N, 4.43 :  
Found. C, 68.18 ; H, 6.93 ; N, 4.53  
Reference Example 164

In DMF (82ml) was dissolved 4-bromo-2,3-dimethylphenol (8.2g). To the mixture were added potassium carbonate (7.3g) and sodium iodide (6.1g) and then was added dropwise 2-chloroethylpropylether (6.2ml), and the mixture was stirred at 90°C for 10 hours and cooled to room temperature. The reaction mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography

(hexane/ethyl acetate=12/1) to give 4-bromo-2,3-dimethyl-1-(2-propoxyethoxy)benzene (7.5g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J=7.4Hz), 1.55-1.70 (2H, m), 2.20 (3H, s), 2.36 (3H, s), 3.50 (2H, t, J=6.6Hz), 3.75-3.81 (2H, m), 4.03-4.10 (2H, m), 6.60 (1H, d, J=8.8Hz), 7.21 (1H, d, J=8.4Hz)

#### Reference Example 165

To a solution of magnesium (0.62g) in THF (9.3ml) was added 1,2-dibromoethane (3 drops). While refluxing the mixture, a solution of 4-bromo-2,3-dimethyl-1-(2-propoxyethoxy)benzene (7.0g) in THF (56ml) was gradually added dropwise to the mixture, and the mixture was stirred for 15 minutes and cooled to -78°C. To the mixture was added dropwise a solution of trimethyl borate (3.8g) in THF (3.8ml), and the mixture was gradually warmed to room temperature and stirred at room temperature for 6 hours. To the mixture was added 2N hydrochloric acid (28ml), and the mixture was stirred for 15 minutes, extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane/isopropylether to give 2,3-dimethyl-4-(2-propoxyethoxy)phenyl borate (3.8g). <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.89 (3H, t, J=7.2Hz), 1.46-1.61 (2H, m), 2.08 (3H, s), 2.31 (3H, s), 3.44 (2H, t, 6.6Hz), 3.68-3.74 (2H, m), 4.02-4.07 (2H, m), 6.72 (1H, d, J=8.4Hz), 7.22 (1H, d, J=8.2Hz), 7.75 (2H, br)

#### Working Example 125 (Production of Compound 122)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) was added toluene/ethanol/water (20/1/1, 13.9ml) and then were added 3-trifluoromethylphenyl borate (174mg) and potassium carbonate (176mg), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was refluxed for 14 hours and cooled to room

temperature. The mixture was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol =4/1) and recrystallized from ethanol to give 7-[2,3-dimethyl-4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino)methyl]phenyl]1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 122) (211mg).

m.p. 158-159°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.4Hz), 1.55-1.83 (6H, m), 2.16 (3H, s), 2.20 (3H, s), 2.24 (3H, s), 2.64 (1H, m), 3.19 (2H, t, J=6.4Hz), 3.30-3.43 (2H, m), 3.53 (2H, t, J=6.6Hz), 3.57 (2H, s), 3.69-3.76 (2H, m), 3.84 (2H, t, J=4.8Hz), 3.97-4.09 (2H, m), 4.16 (2H, t, J=4.8Hz), 6.80 (1H, d, J=8.4Hz), 7.00 (1H, d, J=8.4Hz), 7.28-7.38 (5H, m), 7.43 (1H, dd, J=8.0, 1.4Hz), 7.53 (1H, d, J=8.4Hz), 7.87 (1H, s), 8.18 (1H, d, J=8.0Hz)

IR(KBr) 3331, 2942, 1651, 1593, 1518, 1408, 1289, 1130, 1096, 820cm<sup>-1</sup>

Anal. for C<sub>33</sub>H<sub>46</sub>N<sub>2</sub>O<sub>6</sub>S Calcd. C, 68.70 ; H, 7.17 ; N, 4.33 : Found. C, 68.70 ; H, 7.19 ; N, 4.09

#### 25 Reference Example 166

A mixture of triphenylphosphine (33g) and 2-bromoethylethyl ether (25g) was stirred at 140°C for 1 hour and cooled to precipitate crystals (51.5g), which were collected by filtration and washed with acetone and diethylether. The obtained crystals (27g) and p-bromobenzaldehyde (8g) were suspended in DMSO (25ml) and THF (500ml). To the suspension was added under ice-cooling potassium t-butoxide (7.3g), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 hour, poured into ice-water, concentrated and extracted with ethyl acetate. The organic layer was washed with and saturated

brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (hexane/diethylether) to give colorless oil (5.6g), which was dissolved in ethyl acetate (150ml). The mixture was subjected to reduction with 5% palladium carbon (0.6g) at room temperature for 4 hours. The catalyst was filtered off, and the solvent of the filtrate was evaporated. The residue was distilled under reduced pressure to give 1-bromo-4-(3-ethoxypropyl)benzene (3.3g) as colorless oil.

b.p. 104-111°C/3mmHg.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.21 (3H, t, J=6.9Hz), 1.79-1.93 (2H, m), 2.65 (2H, t, J=7.7Hz), 3.37-3.52 (4H, m), 7.07 (2H, d, J=8.4Hz), 7.39 (2H, d, J=8.4Hz).

Reference Example 167

In THF (5ml) was suspended magnesium (0.37g), and to the suspension was added under nitrogen atmosphere dibromoethane (catalytic amount) and then was added dropwise a solution of 1-bromo-4-(3-ethoxypropyl)benzene (3.4g) in THF (30ml). The mixture was stirred at 50°C for 1.5 hours and cooled with dry ice/acetone. To the mixture was added dropwise trimethyl borate (3.1ml), and the mixture was stirred at room temperature overnight. To the mixture was added 1N hydrochloric acid, and the mixture was stirred at room temperature for 30 minutes, concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give 4-(3-ethoxypropyl)phenyl borate (1.2g) as pale yellow oil.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.23 (3H, t, J=7.0Hz), 1.90-2.00 (2H, m), 2.79 (2H, t, J=7.7Hz), 3.42-3.55 (4H, m), 7.34 (2H, d, J=7.6Hz), 8.16 (2H, d, J=7.6Hz).

Reference Example 168

A solution of 4-bromo-2,6-dimethylphenol (20g) in DMF



(100ml) was added dropwise to a suspension of 60% sodium hydride (4.4g) in DMF (50ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature for 2 hours. To the mixture were added  
5 bromoethylethyl ether (12.3ml) and sodium iodide (16.4g), and the mixture was stirred at 75°C overnight. The mixture was poured into water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate.  
10 The solvent was evaporated, and the residue was distilled under reduced pressure to give 5-bromo-2-(2-ethoxyethoxy)-1,3-dimethylbenzene (24.1g) as colorless oil.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.25 (3H, t, J=7.0Hz), 2.26 (6H, s), 3.60  
15 (2H, q, J=7.0Hz), 3.72-3.77 (2H, m), 3.88-3.93 (2H, m), 7.13 (2H, s).

#### Reference Example 169

In THF (100ml) was suspended magnesium (2.36g). To the suspension was added under nitrogen atmosphere  
20 dibromoethane (catalytic amount) and then was added dropwise a solution of 5-bromo-2-(2-ethoxyethoxy)-1,3-dimethylbenzene (24.1g) in THF (100ml). The mixture was stirred at 55°C for 2.5 hours and cooled with dry ice/acetone.

To the mixture was added dropwise trimethyl borate (19.8ml),  
25 and the mixture was stirred at room temperature was stirred overnight. To the mixture was added 1N hydrochloric acid, and the mixture was stirred at room temperature for 30 minutes, concentrated and extracted with ethyl acetate.

The organic layer was washed with water and saturated brine,  
30 and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 4-(2-ethoxyethoxy)-3,5-dimethylphenyl borate (8.4g) as colorless crystals.

<sup>1</sup>H-NMR(δ ppm, DMSO-d<sub>6</sub>) 1.16 (3H, t, J=7.2Hz), 2.21 (3H, s),  
2.26 (3H, s), 3.46 (2H, q, J=7.2Hz), 3.65-3.69 (2H, m),  
35 3.85-3.90 (2H, m), 7.48 (2H, s).

#### Reference Example 170

A suspension of 4-bromo-2-ethoxyphenol (8g), 1-bromopropane (4ml), sodium iodide (5.5g) and potassium carbonate (10.2g) in DMF (100ml) was stirred under nitrogen atmosphere at 75°C overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was distilled under reduced pressure to give 1-bromo-3-ethoxy-4-propoxybenzene (8.5g) as pale yellow oil. b.p. 109-113°C/2mmHg.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.03 (3H, t, J=7.5Hz), 1.44 (3H, t, J=7.0Hz), 1.77-1.89 (2H, m), 3.90-4.11 (4H, m), 6.74 (1H, d, J=9.2Hz), 6.96-7.02 (2H, m).

Reference Example 171

In THF (5ml) was suspended magnesium (0.88g). To the suspension was added under nitrogen atmosphere dibromoethane (catalytic amount), and then was added dropwise a solution of 1-bromo-3-ethoxy-4-propoxybenzene (8.5g) in THF (30ml). The mixture was stirred at 50°C for 1 hour and cooled with dry ice/acetone. To the mixture was added dropwise trimethyl borate (7.4ml), and the mixture was stirred at room temperature was stirred overnight. To the mixture was added 1N hydrochloric acid, and the mixture was stirred at room temperature for 30 minutes, concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 3-ethoxy-4-propoxyphenyl borate (4.7g) as colorless crystals.

<sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 0.98 (3H, t, J=7.5Hz), 1.32 (3H, t, J=6.9Hz), 1.67-1.78 (2H, m), 3.89-4.06 (4H, m), 6.90 (1H, d, J=8.4Hz), 7.32-7.37 (2H, m), 7.82 (2H, s).

Reference Example 172

A suspension of 4-bromo-2-ethoxyphenol (8g), bromoethylethyl ether (5ml), sodium iodide (5.5g) and

potassium carbonate (10.2g) in DMF (100ml) was stirred under nitrogen atmosphere at 90°C overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was distilled under reduced pressure to give 1-bromo-3-ethoxy-4-(2-ethoxyethoxy)benzene (8.1g) as yellow oil.

b.p. 131-134°C/2mmHg.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.23 (3H, t, J=7.2Hz), 1.44 (3H, t, J=7.0Hz), 3.61 (2H, q, J=7.0Hz), 3.79 (2H, t, J=5.2Hz), 4.00-4.16 (4H, m), 6.80 (1H, d, J=8.8Hz), 6.96-7.02 (2H, m).

Reference Example 173

In THF (5ml) was suspended magnesium (0.79g). To the suspension was added under nitrogen atmosphere dibromoethane (catalytic amount) and then was added dropwise a solution of 1-bromo-3-ethoxy-4-(2-ethoxyethoxy)benzene (8.1g) in THF (30ml). The mixture was stirred at 50°C for 1 hour and cooled with dry ice/acetone. To the mixture was added dropwise trimethyl borate (6.6ml), and the mixture was stirred at room temperature was stirred overnight. To the mixture was added 1N hydrochloric acid, and the mixture was stirred at room temperature for 30 minutes, concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 3-ethoxy-4-(2-ethoxyethoxy)phenyl borate (2.1g) as pale red crystals.

<sup>1</sup>H-NMR(δ ppm, DMSO-d<sub>6</sub>) 1.13 (3H, t, J=6.9Hz), 1.32 (3H, t, J=6.9Hz), 3.52 (2H, q, J=6.9Hz), 3.67-3.72 (2H, m), 3.97-4.10 (4H, m), 6.92 (1H, d, J=7.8Hz), 7.32-7.39 (2H, m), 7.84 (2H, s).

Reference Example 174

A suspension of 4-bromocatechol (9.7g),

chloroethylethyl ether (13.3ml), sodium iodide (15.4g) and potassium carbonate (21.3g) in DMF (100ml) was stirred under nitrogen atmosphere at 85°C overnight. The solvent was evaporated, and to the residue was added water. The mixture  
5 was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was distilled under reduced pressure to give 1-bromo-3,4-bis(2-ethoxyethoxy)benzene (12.7g) as orange  
10 oil.

b.p. 154-161°C/1.5mmHg.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.23 (6H, t, J=7.2Hz), 3.60 (4H, q, J=7.2Hz), 3.76-3.82 (4H, m), 4.10-4.16 (4H, m), 6.79 (1H, d, J=8.0Hz), 7.02 (1H, dd, J=2.2, 8.0Hz), 7.04 (1H, s).

15 Reference Example 175

In THF (10ml) was suspended magnesium (1.0g). To the suspension was added under nitrogen atmosphere dibromoethane (catalytic amount) and then was added dropwise a solution of 1-bromo-3,4-bis(2-ethoxyethoxy)benzene  
20 (12.7g) in THF (80ml). The mixture was stirred at 50°C for 1 hour and cooled with dry ice/acetone. To the mixture was added dropwise trimethyl borate (8.5ml), and the mixture was stirred at room temperature was stirred overnight. To the mixture was added 1N hydrochloric acid, and the mixture  
25 was stirred at room temperature for 30 minutes, concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column  
30 chromatography (ethyl acetate/methanol/triethylamine) to give 3,4-bis(2-ethoxyethoxy)phenyl borate (1.65g) as colorless crystals.

<sup>1</sup>H-NMR(δ ppm, DMSO-d<sub>6</sub>) 1.07-1.17 (6H, m), 3.44-3.58 (4H, m), 3.67-3.71 (4H, m), 4.01-4.11 (4H, m), 6.93 (1H, d, J=8.0Hz),  
35 7.34-7.41 (2H, m), 7.85 (2H, s).

Working Example 126 (Production of Compound 123)

A mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.3g), 4-(3-ethoxypropyl)phenyl borate (0.18g), 1M potassium carbonate solution (1.3ml), ethanol (1.3ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed under argon atmosphere for 6 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethanol to give 7-[4-(3-ethoxypropyl)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 123) (0.25g) as colorless crystals. mp 217-219°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.23 (3H, t, J=7.0Hz), 1.60-1.86 (4H, m), 1.87-2.01 (2H, m), 2.21 (3H, s), 2.59-2.73 (1H, m), 2.77 (2H, t, J=7.9Hz), 3.18 (2H, t, J=6.7Hz), 3.33-3.55 (6H, m), 3.57 (2H, s), 3.72 (2H, t, J=6.7Hz), 4.01-4.07 (2H, m), 7.31-7.35 (4H, m), 7.51-7.56 (4H, m), 7.66 (1H, s), 7.70 (1H, d, J=8.2Hz), 7.80 (1H, s), 8.21 (1H, d, J=8.2Hz). IR(KBr) ν: 2946, 2853, 1657, 1597, 1518cm<sup>-1</sup>. Anal. calcd. for C<sub>33</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>S: C, 69.74; H, 7.02; N, 4.65. Found C, 69.47; H, 7.26; N, 4.61.

30 Working Example 127 (Production of Compound 124)

A mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.3g), 4-(2-ethoxyethoxy)-3,5-dimethylphenyl borate (0.16g), 1M potassium carbonate solution (1.3ml), ethanol (1.3ml) and toluene (25ml) was stirred under argon atmosphere at room

temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed under argon atmosphere for 6 hours and extracted with ethyl acetate. The organic layer was washed  
5 with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to precipitate crude crystals, which were collected by filtration, washed with ethyl acetate/hexane, recrystallized from ethanol to give 7-[4-(2-  
10 ethoxyethoxy)-3,5-dimethylphenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 124) (0.32g) as colorless crystal.  
mp 211-212°C.

15 <sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.27 (3H, t, J=7.0Hz), 1.59-1.77 (4H, m), 2.21 (3H, s), 2.37 (6H, s), 2.58-2.70 (1H, m), 3.17 (2H, t, J=6.6Hz), 3.37 (2H, dt, J=3.0, 11.0Hz), 3.57 (2H, s), 3.61-3.82 (6H, m), 3.97-4.06 (4H, m), 7.25-7.35 (4H, m), 7.54 (2H, d, J=8.4Hz), 7.63 (1H, s), 7.66 (1H, dd, J=1.8,  
20 9.8Hz), 7.79 (1H, s), 8.19 (1H, d, J=8.0Hz).  
IR(KBr) ν: 2928, 2841, 1669, 1597, 1520cm<sup>-1</sup>.  
Anal. calcd. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>6</sub>S: C, 68.33; H, 7.01; N, 4.43. Found C, 68.23; H, 6.95; N, 4.38.

Working Example 128 (Production of Compound 125)

25 A mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.3g), 3-ethoxy-4-propoxyphenyl borate (0.16g), 1M potassium carbonate solution (1.3ml), ethanol (1.3ml) and toluene  
30 (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed under argon atmosphere for 6 hours and extracted with ethyl acetate. The organic layer was washed  
35 with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the

residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethanol to give  
 5 7-(3-ethoxy-4-propoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 125) (0.16g) as colorless crystals.  
 mp 203-205°C.

10 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.07 (3H, t, J=7.5Hz), 1.48 (3H, t, J=6.7Hz), 1.64-1.94 (6H, m), 2.21 (3H, s), 2.60-2.71 (1H, m), 3.17 (2H, t, J=6.7Hz), 3.37 (2H, dt, J=2.4, 10.9Hz), 3.58 (2H, s), 3.71 (2H, t, J=6.7Hz), 3.74-4.22 (6H, m), 6.97 (1H, d, J=8.0Hz), 7.11-7.18 (2H, m), 7.31-7.35 (3H, m), 7.52-7.64 (4H, m), 7.94 (1H, s), 8.16 (1H, d, J=8.0Hz).  
 15 IR(KBr) ν: 2940, 2845, 1669, 1595, 1516cm<sup>-1</sup>.  
 Anal. calcd. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S·0.2H<sub>2</sub>O: C, 67.54; H, 6.87; N, 4.50. Found C, 67.44; H, 6.67; N, 4.50.

Working Example 129 (Production of Compound 126)

A mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.3g),  
 20 3-ethoxy-4-(2-ethoxyethoxy)phenyl borate (0.18g), 1M potassium carbonate solution (1.3ml), ethanol (1.3ml) and toluene (25ml) was stirred under argon atmosphere at room  
 25 temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed under argon atmosphere for 6 hours and extracted with ethyl acetate. The organic layer was washed  
 30 with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude  
 35 N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide

(Compound 126) (0.26g) as colorless crystals.

mp 164-168°C.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.24 (3H, t, J=7.0Hz), 1.47 (3H, t, J=7.0Hz), 1.61-1.75 (4H, m), 2.21 (3H, s), 2.59-2.75 (1H, m), 3.17 (2H, t, J=6.9Hz), 3.38 (2H, dt, J=3.6, 11.2Hz), 3.57 (2H, s), 3.61-3.74 (4H, m), 3.85 (2H, t, J=4.9Hz), 4.01-4.23 (6H, m), 6.98-7.14 (3H, m), 7.30-7.35 (3H, m), 7.53-7.65 (4H, m), 7.88 (1H, s), 8.17 (1H, d, J=8.0Hz). IR(KBr) ν: 2946, 2843, 1661, 1599, 1518cm<sup>-1</sup>.

Anal. calcd. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>7</sub>S: C, 66.64; H, 6.84; N, 4.32. Found C, 66.44; H, 6.99; N, 4.19.

Working Example 130 (Production of Compound 127)

A mixture of 7-bromo-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.3g), 3,4-bis(2-ethoxyethoxy)phenyl borate (0.23g), 1M potassium carbonate solution (1.3ml), ethanol (1.3ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed under argon atmosphere for 6 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethanol to give 7-[3,4-bis(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 127) (0.3g) as colorless crystals. mp 150-151°C.

<sup>1</sup>H-NMR(δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J=7.0Hz), 1.23 (3H, t, J=6.9Hz), 1.64-1.75 (4H, m), 2.21 (3H, s), 2.59-2.70 (1H, m), 3.18 (2H, t, J=6.4Hz), 3.38 (2H, dt, J=2.6, 11.1Hz), 3.55-3.73 (8H, m), 3.79-3.84 (4H, m), 4.01-4.08 (2H, m),



4.19-4.27 (4H, m), 6.99 (1H, d, J=8.0Hz), 7.11-7.19 (2H, m), 7.30-7.34 (3H, m), 7.55-7.63 (4H, m), 7.99 (1H, s), 8.16 (1H, d, J=8.0Hz).

IR(KBr)  $\nu$ : 2975, 2960, 2880, 1665, 1597, 1516 $\text{cm}^{-1}$ .

- 5 Anal. calcd. for  $\text{C}_{36}\text{H}_{48}\text{N}_2\text{O}_8\text{S}$ : C, 65.87; H, 6.98; N, 4.04. Found C, 65.65; H, 6.90; N, 4.16.

Reference Example 176

- To a solution of p-bromophenol (10.0g), 3-methoxy-3-methylbutanol (8.2g) and triphenylphosphone (18.2g) in 10 tetrahydrofuran (60ml) was added dropwise under nitrogen atmosphere at 0°C diethylazodicarbonate (40% toluene solution, 12.1g) for 15 minutes, and the mixture was allowed to warm to room temperature, stirred for 16 hours and concentrated under reduced pressure. To the residue was 15 added diethylether, and insoluble materials were filtered off. The filtrate was washed with 1N sodium hydroxide solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel 20 column chromatography (ethyl acetate/hexane 1:5) to give yellow oil of 4-bromo-(3-methoxy-3-methyl)butoxybenzene (15.4g).

- $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23 (6H, s), 1.98 (2H, t, J=7.4 Hz), 3.21 (3H, s), 4.02 (2H, t, J=6.0 Hz), 6.78 (2H, dd, 25 J=8.0, 2.2 Hz), 7.36 (2H, dd, J=9.2, 2.2 Hz).

Reference Example 177

- To a mixture of magnesium (1.39g), 1,2-dibromoethane (0.15ml) and anhydrous tetrahydrofuran (50ml) was added dropwise under argon atmosphere a solution of 4-bromo-30 (3-methoxy-3-methyl)butoxybenzene (15.0g) in anhydrous tetrahydrofuran (100ml) for 1 hour, and the mixture was stirred at 60°C for 1 hour. To the mixture was added dropwise at -78°C a solution of trimethyl borate (11.5g) in anhydrous tetrahydrofuran (20ml), and the mixture was stirred at room 35 temperature for 2 hours. To the mixture was added at 0°C 3N hydrochloric acid, and the mixture was stirred for 30

minutes and extracted with ethyl acetate (twice). The organic layer was washed with saturated brine (twice) and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give solid, which was washed with  
5 hexane (20ml) and dried in vacuo to give colorless solid of 4-(3-methoxy-3-methyl)butoxyphenyl borate (5.7g). The filtrate obtained by washing with hexane was purified with silica gel column chromatography to give 4-(3-methoxy-3-methyl)butoxyphenyl borate (0.8g).  
10 <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 1.17 (6H, s), 1.91 (2H, t, J=7.0 Hz), 3.12 (3H, s), 4.04 (2H, t, J=7.4 Hz), 6.88 (2H, d, J=8.4 Hz), 7.72 (2H, d, J=8.4 Hz), 7.83 (2H, s).

## Reference Example 178

To a solution of o-cresol (6.0g) in dichloromethane  
15 (120ml) and methanol (80ml) was added little by little the solid of tetrabutylammonium tribromide (27.0g), and the mixture was stirred for 1 hour and concentrated under reduced pressure. To the residue was added water, and the mixture was extracted with ether (4 times). The organic layer was  
20 washed with saturated brine (twice) and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give solid, which was dried in vacuo to give colorless solid of 4-bromo-2-methylphenol (9.3g).  
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.22 (3H, s), 4.96 (1H, s), 6.65  
25 (1H, d, J=8.4 Hz), 7.15 (1H, dd, J=8.4, 1.8 Hz), 7.24 (1H, d, J=1.8 Hz).

## Reference Example 179

To a solution of 4-bromo-2-methylphenol (9.3g) in DMF (50ml) was added potassium carbonate (9.62g) and then was  
30 added dropwise 2-bromoethyl ethyl ether (7.99g), and the mixture was stirred at 70°C for 3 days. To the mixture was added dropwise 2-bromoethyl ethyl ether (1.52g), and the mixture was stirred at 70°C for 4.5 hours and cooled. To the mixture was added water, and the mixture was extracted  
35 with ether. The organic layer was washed with 1N sodium hydroxide solution and saturated brine, and dried with

magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was distilled under reduced pressure (3mmHg, 170°C) to give colorless oil of 4-bromo-2-methyl-(2-ethoxyethoxy)benzene (10.6g).

- 5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.24 (3H, t, J=6.0 Hz), 2.21 (3H, s), 3.61 (2H, q, J=6.2 Hz), 3.79 (2H, t, J=3.4 Hz), 4.09 (2H, t, J=4.6 Hz), 6.69 (1H, d, J=9.0 Hz), 7.20-7.26 (2H, m).

Reference Example 180

- 10 To a mixture of magnesium (966mg), 1,2-dibromoethane (0.1ml) and anhydrous tetrahydrofuran (35ml) was added dropwise under argon atmosphere a solution of 4-bromo-2-methyl-(2-ethoxyethoxy)benzene (10.0g) in anhydrous tetrahydrofuran (70ml) for 1 hour, and the mixture was  
15 stirred at 70°C for 1 hour and 20 minutes. To the mixture was added dropwise at 0°C a solution of trimethyl borate (8.0g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred at room temperature for 16 hours. To the mixture was added at 0°C 1N hydrochloric acid (200ml), and the  
20 mixture was stirred for 30 minutes and extracted with ethyl acetate (twice). The organic layer was washed with saturated brine (twice) and dried with magnesium sulfate.

- Under reduced pressure, the solvent was evaporated to give solid, which was washed with hexane (40ml) and dried in vacuo  
25 to give colorless solid of 4-(2-ethoxyethoxy)-3-methylphenyl borate (3.5g).

- <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 1.13 (3H, t, J=7.0 Hz), 2.14 (3H, s), 3.51 (2H, q, J=7.2 Hz), 3.71 (2H, t, J=4.4 Hz), 4.09 (2H, t, J=4.6 Hz), 6.87 (1H, d, J=8.0 Hz), 7.50-7.61 (2H, m), 7.75 (2H, s).

Reference Example 181

- To a solution of 3-chloro-2,2-dimethylpropanol (5.0g) and 2,3-dihydropyran (4.12g) in ethyl acetate (20ml) was added camphor sulfonic acid (57mg), and the mixture was  
35 stirred for 19 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic

layer was washed with 0.1N sodium hydroxide solution and saturated brine, and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and distilled under reduced pressure (2mmHg, 108°C) to give colorless oil of 2-(3-chloro-2,2-dimethylpropoxy)tetrahydropyran (6.07g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.01 (6H, d, J=4.8 Hz), 1.43-1.90 (6H, m), 3.15 (1H, d, J=9.2 Hz), 3.42-3.59 (4H, m), 3.80-3.91 (1H, m), 4.60 (1H, t, J=2.8 Hz).

10 Reference Example 182

Sodium hydride (60% oil, 1.34g) was washed with hexane (thrice), to which was added DMF (50ml). To the mixture was added dropwise a solution of p-bromophenol (4.82g) in DMF (50ml) at 0°C, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added dropwise at 0°C a solution of 2-(3-chloro-2,2-dimethylpropoxy)tetrahydropyran (4.8g) in DMF (30ml) and then was added sodium iodide (4.9g), and the mixture was stirred at 165°C for 3 days and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with 1N sodium hydroxide solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:hexane=1:10 to give colorless oil of 4-bromo-[2,2-dimethyl-3-(2-tetrahydropyranoxy)propoxy]benzene (7.37g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.03 (6H, d, J=2.6 Hz), 1.45-1.79 (6H, m), 3.20 (1H, d, J=9.4 Hz), 3.43-3.52 (1H, m), 3.62 (1H, d, J=9.2 Hz), 3.66-3.82 (3H, m), 4.55 (1H, t, J=3.0Hz), 6.79 (2H, dd, J=8.8, 2.2 Hz), 7.35 (2H, dd, J=9.2, 2.2 Hz).

Reference Example 183

To a solution of 4-bromo-[2,2-dimethyl-3-(2-tetrahydropyranoxy)propoxy]benzene (7.37g) in methanol (80ml) was added p-toluenesulfonic acid (205mg), and the mixture was stirred at room temperature for 15.5 hours. To

the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:hexane=1:5 to give colorless crystals of 4-bromo-(2,2-dimethyl-3-hydroxy)propoxybenzene (4.80g). <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.02 (6H, s), 1.74 (1H, t, J=4.8 Hz), 3.54 (2H, d, J=5.8 Hz), 3.73 (2H, s), 6.79 (2H, dd, J=8.8, 2.2 Hz), 7.37 (2H, dd, J=9.2, 2.2 Hz). Anal. for C<sub>11</sub>H<sub>15</sub>O<sub>2</sub>Br Calcd. C, 50.98 ; H, 5.83 : Found. C, 50.93 ; H, 6.01.

#### Reference Example 184

Sodium hydride (60%oil, 1.28g) was washed with hexane (thrice), to which was added DMF (40ml). To the mixture was added dropwise at 0°C a solution of 4-bromo-(2,2-dimethyl-3-hydroxy)butoxybenzene (4.5g) in DMF (50ml) under nitrogen atmosphere, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added dropwise at 0°C a solution of iodoethane (7.82g) in DMF (80ml), and the mixture was stirred at room temperature for 16 hours. To the mixture was added water, and the mixture was extracted with hexane. The organic layer was washed with 1N sodium hydroxide solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:hexane=1:5 to give colorless oil of 4-bromo-(2,2-dimethyl-3-ethoxy)propoxybenzene (7.37g). <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.00 (6H, s), 1.14 (3H, t, J=7.0 Hz), 3.25 (2H, s), 3.44 (2H, q, J=7.4 Hz), 3.69 (2H, s), 6.79 (2H, dd, J=9.0, 2.2 Hz), 7.35 (2H, dd, J=9.2, 2.2 Hz).

#### Reference Example 185

To a mixture of magnesium (262mg), 1,2-dibromoethane (0.05ml) and anhydrous tetrahydrofuran (25ml) was added dropwise under nitrogen atmosphere a solution of 4-

bromo-(2,2-dimethyl-3-ethoxy)propoxybenzene (3.0g) in anhydrous tetrahydrofuran (25ml) for 30 minutes, and the mixture was stirred at 70°C for 3 hours and cooled to -78°C.

To the mixture was added dropwise at -78°C a solution of trimethyl borate (2.17g) in anhydrous tetrahydrofuran (10ml), and the mixture was stirred at room temperature for 19 hours. To the mixture was added at 0°C 1N hydrochloric acid (50ml), and the mixture was stirred for 30 minutes and extracted with ethyl acetate (thrice). The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:hexane=1:1 to give colorless solid of 4-(2,2-dimethyl-3-ethoxy)propoxyphenyl borate (505mg).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 0.96 (6H, s), 1.07 (3H, t, J=7.0 Hz), 3.23 (2H, s), 3.40 (2H, q, J=7.0 Hz), 3.71 (2H, s), 6.88 (2H, t, J=7.5 Hz), 7.69 (2H, t, J=7.6 Hz), 7.80 (2H, s).

Reference Example 186

To a solution of 4-bromo-3-chlorophenol (10.0g), 3-ethoxypropanol (6.0g) and triphenylphosphine (15.2g) in tetrahydrofuran (50ml) was added dropwise under nitrogen atmosphere at 0°C diethylazodicarbonate (40% toluene solution, 25.2g) for 15 minutes, and the mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. To the residue was added diethylether, and insoluble materials were filtered off. The filtrate was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane 1:5) and distilled under reduced pressure (1.5mmHg, 190°C) to give colorless oil of 4-bromo-3-chloro-(3-ethoxypropoxy)benzene (11.2g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.19 (3H, t, J=7.0 Hz), 2.08 (2H, m), 3.50 (2H, q, J=7.4 Hz), 3.62 (2H, t, J=6.2 Hz), 4.11

(2H, t, J=3.6 Hz), 6.82 (1H, d, J=8.8 Hz), 7.31 (1H, dd, J=8.4, 2.2 Hz), 7.49 (1H, d, J=2.2 Hz).

Reference Example 187

- To a mixture of magnesium (853mg), 1,2-dibromoethane (0.2ml) and anhydrous tetrahydrofuran (35ml) was added dropwise under nitrogen atmosphere a solution of 4-bromo-3-chloro-(3-ethoxypropoxy)benzene (10.0g) in anhydrous tetrahydrofuran (70ml) for 50 minutes, and the mixture was stirred at 65°C for 2.5 hours and cooled to -78°C.
- To the mixture was added dropwise at -78°C a solution of trimethyl borate (7.08g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred at room temperature for 19 hours. To the mixture was added at 0°C 1N hydrochloric acid (50ml), and the mixture was stirred for 30 minutes and extracted with ethyl acetate (thrice). The organic layer was washed with saturated brine (twice) and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the solid washed with hexane (35ml) to give colorless solid of 3-chloro-4-(3-ethoxypropoxy)phenyl borate (5.65g).

- <sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 1.10 (3H, t, J=7.0 Hz), 1.97 (2H, m), 3.43 (2H, q, J=7.0 Hz), 3.53 (2H, t, J=6.2 Hz), 4.12 (2H, t, J=6.2 Hz), 7.10 (1H, d, J=8.4 Hz), 7.71 (1H, dd, J=8.0, 1.6 Hz), 7.79 (1H, d, J=1.4 Hz), 8.03 (2H, s).
- Working Example 131 (Production of Compound 128)

- In toluene (10ml), ethanol (1ml) and water (1ml) were suspended 4-(3-methoxy-3-methyl)butoxyphenyl borate (119mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (200mg) and potassium carbonate (138mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (31mg), and the mixture was stirred under argon atmosphere at 100°C for 8 hours and cooled. To the mixture was added saturated brine, and the mixture was extracted with ethyl acetate (twice).

- The organic layer was dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:methanol=3:1) and recrystallized from ethanol (19ml) to give colorless crystals of 7-[4-(3-methoxy-3-methyl)butoxyphenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 128) (136mg).
- 10 m.p. 204.5-205.5 °C
- <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (6H, s), 1.75 (4H, br), 2.04 (2H, t, J=6.8 Hz), 2.21 (3H, s), 3.17 (2H, t, J=7.2 Hz), 3.24 (3H, s), 3.37 (2H, dt, J=11.0, 2.2 Hz), 3.58 (2H, s), 3.73 (2H, t, J=7.4 Hz), 4.02-4.17 (4H, m), 7.01 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.52-7.57 (4H, m), 7.63-7.70 (2H, m), 8.20 (1H, d, J=8.4 Hz).
- 15 Anal. for C<sub>36</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>S Calcd. C, 68.33 ; H, 7.01 ; N, 4.43 ; Found. C, 68.03 ; H, 6.78 ; N, 4.33.
- Working Example 132 (Production of Compound 129)
- 20 In toluene (10ml), ethanol (1ml) and water (1ml) were suspended 4-(2-ethoxyethoxy)-3-methylphenyl borate (119mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (212mg) and potassium
- 25 carbonate (147mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (33mg), and the mixture was stirred under argon atmosphere at 100°C for 8 hours and cooled. To the mixture was added saturated brine,
- 30 and the mixture was extracted with ethyl acetate (twice). The organic layer was dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:methanol=7:1) and recrystallized from
- 35 ethanol (22.5ml) to give colorless crystals of 7-[4-(2-ethoxyethoxy)-3-methyl-phenyl]-N-[4-[[N-methyl-N-



(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 129) (131mg).

m.p. 212-213 °C

- 5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J=6.4 Hz), 1.75 (4H, br), 2.21 (3H, s), 2.31 (3H, s), 2.65 (1H, br), 3.16 (2H, t, J=7.0 Hz), 3.38 (2H, dt, J=9.0, 3.0 Hz), 3.57-3.75 (6H, m), 3.85 (2H, t, J=4.4 Hz), 4.04 (2H, d, J=11.2 Hz), 4.19 (2H, t, J=5.2 Hz), 6.92 (2H, d, J=9.2 Hz), 7.26-7.39 (4H, m), 7.54 (2H, d, J=8.8 Hz), 7.62-7.68 (2H, m), 7.87 (1H, s), 8.18 (1H, d, J=8.2 Hz).

Anal. for C<sub>35</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S · 0.1H<sub>2</sub>O Calcd. C, 67.94 ; H, 6.84 ; N, 4.53 ; Found. C, 67.45 ; H, 6.63 ; N, 4.53.

Working Example 133 (Production of Compound 130)

- 15 A mixture of 4-(3-ethoxy-2,2-dimethyl)propoxyphenyl borate (189mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg) was suspended in toluene (15ml), ethanol (1.5ml) and water (1.5ml), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred under argon atmosphere at 100°C for 8 hours and cooled. To the mixture was added saturated brine, and the mixture was extracted with ethyl acetate (twice). The organic layer was dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:methanol=8:1) and recrystallized from ethanol (22.5ml) to give colorless crystals of 7-[4-(3-ethoxy-2,2-dimethylpropoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 130) (175mg).
- 35 m.p. 209-210 °C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.04 (6H, s), 1.16 (3H, t, J=7.2

Hz), 1.76 (4H, br), 2.21 (3H, s), 3.17 (2H, t, J=6.2 Hz), 3.20 (2H, s), 3.38-3.51 (4H, m), 3.58 (2H, s), 3.69-3.79 (4H, m), 4.04 (2H, d, J=11.4 Hz), 7.03 (2H, d, J=8.8 Hz), 7.31-7.35 (3H, m), 7.52-7.70 (6H, m), 7.85 (1H, s), 8.20 (1H, d, J=8.0 Hz).

Anal. for  $C_{37}H_{46}N_2O_6S$  Calcd. C, 68.70 ; H, 7.17 ; N, 4.33 ; Found. C, 68.83 ; H, 7.25 ; N, 4.36.

Working Example 134 (Production of Compound 131)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 3-chloro-4-(3-ethoxypropoxy)phenyl borate (194mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg). Under argon atmosphere, the suspension was stirred for 30 minutes, and to the mixture was added tetrakis(triphenylphosphine)palladium (47mg). Under argon atmosphere, the mixture was heated at 100°C for 8 hours and cooled. To the mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate:ethanol=18:1) and recrystallized from ethanol (23ml) to give colorless crystals of 7-[3-chloro-4-(3-ethoxypropoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 131) (229mg).

m.p. 182-183 °C

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  1.21 (3H, t, J=6.8 Hz), 1.75 (4H, m), 2.14 (2H, m), 2.21 (3H, s), 2.65 (1H, m), 3.17 (2H, t, J=7.0 Hz), 3.31-3.76 (10H, m), 4.04 (2H, d, J=11.4 Hz), 4.21 (2H, t, J=6.6 Hz), 7.05 (1H, d, J=8.4 Hz), 7.31-7.35 (3H, m), 7.43-7.68 (6H, m), 7.88 (1H, s), 8.21 (1H, d, J=8.0 Hz).

Reference Example 188

In DMF (98ml) was dissolved 4-bromo-3-chlorophenol

(9.8g), and to the solution were added at room temperature potassium carbonate (9.8g), sodium iodide (7.8g) and 2-chloroethylpropylether (7.8ml). The mixture was stirred at 90°C for 16 hours, cooled to room temperature, poured into  
5 water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate.

Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 1-bromo-2-chloro-4-

10 (2-propoxyethoxy)benzene (8.8g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93(3H, t, J=7.4Hz), 1.55-1.70(2H, m), 3.48(2H, t, J=6.6Hz), 3.76(2H, t, J=4.4Hz), 4.08(2H, t, J=4.4Hz), 6.72(1H, dd, J=8.8, 3.0Hz), 7.04(1H, d, J=3.0Hz), 7.46(1H, d, J=9.2Hz)

15 Reference Example 189

In THF (70ml) was dissolved 1-bromo-2-chloro-4-(2-propoxyethoxy)benzene (7.0g), and to the solution was added dropwise at -78°C 1.6M n-butyllithium/hexane (17.3ml). The mixture was stirred for 1 hour, and to the mixture was added  
20 dropwise trimethoxyborane (7.8g). The mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 2N hydrochloric acid (28ml), and the mixture was stirred for 15 minutes. The reaction solution was extracted with ethyl acetate, washed with saturated  
25 brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give 2-chloro-4-(2-propoxyethoxy)phenyl borate (1.70g).

30 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.86(3H, t, J=7.2Hz), 1.43-1.58(2H, m), 3.40(2H, t, 6.6Hz), 3.65-3.71(2H, m), 4.08-4.15(2H, m), 6.84-6.95(1H, m), 7.38(1H, d, J=8.0Hz), 7.84(1H, d, J=8.4Hz), 8.08(2H, br)

Working Example 135 (Production of Compound 132)

35 To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-

benzothiepine-4-carboxamide (0.40g) was added  
toluene/ethanol/water (10/1/1, 19.2ml). To the mixture  
were added 2-chloro-4-(2-propoxyethoxy)phenyl borate  
(0.24g) and potassium carbonate (0.24g), and the mixture  
5 was stirred at room temperature for 30 minutes. To the  
mixture was added tetrakis(triphenylphosphine)palladium  
(45mg), and the mixture was refluxed for 14 hours and cooled  
to room temperature. The reaction solution was poured into  
water, and the mixture was extracted with ethyl acetate,  
10 washed with saturated brine and dried with magnesium sulfate.  
Under reduced pressure, the solvent was removed, and the  
residue was purified with silica gel column chromatography  
(ethyl acetate/ethanol=4/1) and recrystallized from  
ethanol to give 7-[2-chloro-4-(2-propoxyethyl)phenyl]-  
15 N-[4-[[N-methyl-N-(tetrahydropyran-4-  
yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (Compound 132) (206mg).  
m.p. 150-152°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94(3H, t, J=7.4Hz), 1.55-1.82(6H,  
20 m), 2.20(3H, s), 2.64(1H, m), 3.15-3.22(2H, m), 3.30-3.44(2H,  
m), 3.51(2H, t, J=6.6Hz), 3.56(2H, s), 3.72(2H, t, J=6.6Hz),  
3.75-3.84(2H, m), 3.98-4.08(2H, m), 4.17(2H, t, J=4.8Hz),  
6.94(1H, dd, J=8.8, 2.6Hz), 7.08(1H, d, J=2.4Hz), 7.21-  
7.33(4H, m), 7.50-7.60(4H, m), 7.83(1H, s), 8.20(1H, d,  
25 J=8.0Hz)

IR(KBr) 3349, 2959, 1651, 1603, 1516, 1408, 1289, 1128,  
1060, 822cm<sup>-1</sup>

Elemental Analysis for C<sub>35</sub>H<sub>41</sub>FN<sub>2</sub>O<sub>6</sub>S

Calcd. C, 64.35 ; H, 6.33 ; N, 4.29 ;

30 Found. C, 64.17 ; H, 6.24 ; N, 4.22

Reference Example 190

In DMF (90ml) was dissolved 4-bromo-3-fluorophenol  
(9.0g), and to the solution were added at room temperature  
potassium carbonate (9.8g), sodium iodide (7.8g) and 2-  
35 chloroethylpropylether (7.7ml). The mixture was stirred at  
90°C for 16 hours and cooled to room temperature. The

reaction solution was poured into water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was  
5 purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 1-bromo-2-fluoro-4-(2-propoxyethoxy)benzene (8.8g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93(3H, t, J=7.4Hz), 1.54-1.73(2H, m), 3.48(2H, t, J=6.6Hz), 3.74-3.81(2H, m), 4.06-4.13(2H, m), 6.69-6.76(1H, m), 7.37(1H, d, J=8.0Hz), 7.69(1H, d, J=7.2Hz)  
10

#### Reference Example 191

In THF (96ml) was dissolved 1-bromo-2-fluoro-4-(2-propoxyethoxy)benzene (8.0g), and to the solution was added  
15 dropwise at -78°C 1.6Mn-butyllithium/hexane (19.8ml). The mixture was stirred for 1 hour, and to the mixture was added dropwise trimethoxyborane (9.0g). The mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added 2N hydrochloric acid (32ml), and the  
20 mixture was stirred for 15 minutes. The reaction solution was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography  
25 (hexane/ethyl acetate=2/1) to give 2-fluoro-4-(2-propoxyethoxy)phenyl borate (1.17g).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.87(3H, t, J=7.2Hz), 1.46-1.60(2H, m), 3.37-3.45(2H, m), 3.66-3.72(2H, m), 4.08-4.13(2H, m), 6.70-6.77(2H, m), 7.50(1H, d, J=8.0Hz), 7.89(2H, br)  
30

#### Working Example 136 (Production of Compound 133)

To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.35g) was added  
35 toluene/ethanol/water (10/1/1, 16.3ml). To the mixture were added 2-fluoro-4-(2-propoxyethoxy)phenyl borate

(0.20g) and potassium carbonate (0.20g), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (31mg), and the mixture was refluxed for 14 hours and cooled to room temperature. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=4/1) and recrystallized from ethanol to give 7-[2-fluoro-4-(2-propoxyethyl)phenyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 133) (105mg).

m.p. 172-174°C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94(3H, t, J=7.4Hz), 1.58-1.76(6H, m), 2.21 (3H, s), 2.65(1H, m), 3.17(2H, t, J=6.6Hz), 3.32-3.44(2H, m), 3.51(2H, t, J=6.6Hz), 3.57(2H, s), 3.72(2H, t, J=6.2Hz), 3.79-3.84(2H, m), 3.98-4.08(2H, m), 4.17(2H, t, J=4.4Hz), 6.75-6.87(2H, m), 7.30-7.40(4H, m), 7.51-7.67(4H, m), 7.85(1H, s), 8.20(1H, d, J=8.6Hz)  
IR(KBr) 3345, 2940, 1651, 1620, 1520, 1410, 1316, 1288, 1127, 816cm<sup>-1</sup>

Elemental Analysis for C<sub>35</sub>H<sub>41</sub>ClN<sub>2</sub>O<sub>6</sub>S · 0.3H<sub>2</sub>O

Calcd. C, 65.46 ; H, 6.53 ; N, 4.36 ;

Found. C, 65.44 ; H, 6.38 ; N, 4.31

Working Example 137 (Production of Compound 134)

In THF (30ml) was dissolved N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (1.0g). To the solution was added L-tartaric acid (0.36mg), and the mixture was stirred at room temperature for 12 hours. Under reduced pressure, the solvent was removed, and the residue was recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-

propoxyethoxy)phenyl)]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide L-tartrate (Compound 134) (1.7g).

m.p. 116-119°C

- 5 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88(3H, t, J=7.2Hz), 1.42-1.81(6H, m), 2.22(3H, s), 2.79(1H, m), 3.22-3.30(2H, m), 3.39-3.46(2H, m), 3.69-3.82(6H, m), 3.70(2H, s), 3.89-3.97(2H, m), 4.17(2H, s), 4.14-4.19(2H, m), 7.10(2H, d, J=8.8Hz), 7.33(2H, d, J=8.4Hz), 7.55(1H, s), 7.69-7.89(5H, m), 8.05-8.09(2H, m), 10.22(1H, s)
- 10 IR(KBr) 3247, 2965, 1663, 1607, 1518, 1416, 1292, 1252, 1128, 826cm<sup>-1</sup>

Elemental Analysis for C<sub>39</sub>H<sub>48</sub>N<sub>2</sub>O<sub>12</sub>S · 0.2H<sub>2</sub>O

Calcd. C, 60.64 ; H, 6.32 ; N, 3.63 ;

- 15 Found. C, 60.59 ; H, 6.12 ; N, 3.64

Reference Example 192

- In THF (94ml) was dissolved 5-bromo-2-methyl-1,3-benzoxazole (9.4g), and to the solution was added dropwise at -78°C 1.6M n-butyllithium/hexane (30.5ml). The mixture was stirred for 1 hour, and to the mixture was added dropwise a solution of trimethoxyborane (9.2ml) in THF (9.2ml). The mixture was stirred for 30 minutes and warmed to room temperature. To the mixture was added water (37.6ml), and the mixture was stirred for 15 minutes. The reaction solution was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was washed with hexane/isopropylether to give 2-methyl-1,3-benzoxazol-5-yl borate (5.5g).
- 20
- 25

- 30 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 2.17(3H, s), 6.88-6.93(1H, m), 7.14-7.40(1H, m), 7.48-7.56(1H, m), 10.24(2H, br)

Working Example 138 (Production of Compound 135)

- To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.35g) was added toluene/ethanol/water (10/1/1, 16.3ml) and then were added
- 35

2-methyl-1,3-benzoxazol-5-yl borate (0.14g) and potassium carbonate (0.23g), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (31mg), and the mixture was refluxed for 14 hours, cooled to room temperature, poured into water. The mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=4/1) and recrystallized from ethanol to give 7-(2-methyl-1,3-benzoxazol-5-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 135) (110mg).  
m.p. 236-240°C  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.42-1.76(4H, m), 2.10(3H, s), 2.50(3H, s), 3.06(2H, t, J=6.6Hz), 3.20-3.32(2H, m), 3.52(2H, s), 3.75-3.83(2H, m), 3.85-3.94(2H, m), 7.27(2H, d, J=8.2Hz), 7.38(1H, s), 7.65(2H, d, J=8.4Hz), 7.79-7.85(1H, d, J=8.4Hz), 10.15(1H, s)  
IR(KBr) 3256, 2953, 2836, 1655, 1634, 1534, 1412, 1319, 1130, 885, 822cm<sup>-1</sup>

#### Reference Example 193

In THF (57ml) was dissolved 5-bromo-2-(hydroxymethyl)-1-benzofuran (5.7g), and to the solution was added at 0°C 60% sodium hydride (1.4g). The mixture was stirred at room temperature for 1 hour, and to the mixture was added at 0°C 1-bromopropane (3.1ml). The mixture was stirred at 65°C for 16 hours and cooled to room temperature. The reaction solution was poured into water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give 5-bromo-2-(propoxymethyl)-1-benzofuran (5.0g).



<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94(3H, t, J=7.2Hz), 1.56-1.72(2H, m), 3.50(2H, t, J=6.6Hz), 4.59(2H, s), 6.63(1H, S), 7.35-7.36(2H, m), 7.66-7.68(1H, m)

Reference Example 194

- 5           In THF (48ml) was dissolved 5-bromo-2-(propoxymethyl)-1-benzofuran (4.8g), and to the solution was added dropwise at -50°C 1.6M n-butyllithium/hexane (12.3ml). The mixture was stirred for 1 hour, and to the mixture was added dropwise trimethoxyborane (5.6g). The
- 10 mixture was stirred for 30 minutes, warmed to room temperature and stirred for 12 hours. To the mixture was added 2N hydrochloric acid (19.2ml), and the mixture was stirred for 15 minutes. The reaction solution was extracted with ethyl acetate, washed with saturated brine and dried
- 15 with magnesium sulfate. Under reduced pressure, the solvent was removed, and the residue was purified with silica gel column chromatography (hexane/ethyl acetate=2/1) to give 2-(propoxymethyl)-1-benzofuran-5-yl borate (0.22g).

- 20           <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.84(3H, t, J=7.0Hz), 1.40-1.55(2H, m), 3.30-3.36(2H, m), 3.31(2H, s), 4.37-4.41(1H, m), 6.80(1H, s), 7.47(1H, d, J=8.2Hz), 7.72(1H, d, J=8.4Hz), 7.95(2H, br)

Working Example 139 (Production of Compound 136)

- 25           To 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.41g) was added toluene/ethanol/water (10/1/1, 19.2ml) and then were added 2-(propoxymethyl)-1-benzofuran-5-yl borate (0.22g) and
- 30 potassium carbonate (0.24g), and the mixture was stirred at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (45mg), and the mixture was refluxed for 14 hours, cooled to room temperature and poured into water. The mixture was extracted with ethyl
- 35 acetate, washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was

- removed, and the residue was purified with silica gel column chromatography (ethyl acetate/ethanol=4/1) and recrystallized from ethanol to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[2-(propoxymethyl)-1-benzofuran-5-yl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 136) (184mg).
- m.p. 204-206°C
- <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.92(3H, t, J=7.2Hz), 1.30-1.43(2H, m), 1.55-1.77(4H, m), 2.20(3H, s), 2.64(1H, m), 3.17(2H, t, J=6.2Hz), 3.30-3.54(4H, m), 3.57(2H, s), 3.98-4.09(2H, m), 4.39(1H, t, J=6.6Hz), 6.68(1H, s), 7.29-7.37(3H, m), 7.43-7.59(4H, m), 7.66-7.74(3H, m), 8.02(1H, s), 8.21(1H, d, J=8.0Hz)
- IR(KBr) 3254, 2948, 1655, 1599, 1530, 1410, 1316, 1128, 806cm<sup>-1</sup>

## Reference Example 195

- To a solution of 4-bromo-2-methylphenol (14.2g) in DMF (75ml) was added potassium carbonate (14.7g), and to the mixture was added dropwise bromopropane (9.33g). The mixture was stirred at 70°C for 3 hours and cooled, and to the mixture was added water. The mixture was extracted with hexane, and the organic layer was washed with 1N sodium hydroxide solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give colorless oil of 4-bromo-2-methylpropoxybenzene (10.6g).

- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.04 (t, 3H, J=7.4 Hz), 1.73-1.90 (m, 2H), 2.19 (s, 3H), 3.89 (t, 2H, J=6.2 Hz), 6.66 (dd, 1H, J=7.4, 1.8 Hz), 7.19-7.24 (m, 2H).

## Reference Example 196

- To a mixture of magnesium (1.09g), 1,2-dibromoethane (0.2ml) and anhydrous tetrahydrofuran (35ml) was added dropwise, under argon atmosphere, a solution of 4-bromo-2-methylphenol (10.0g) in anhydrous tetrahydrofuran (70ml) for 1 hour, and the mixture was stirred at 65°C for

1 hour and 45 minutes. To the mixture was added dropwise at -78°C a solution of trimethyl borate (9.07g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred for 16 hours while gradually warming to room temperature. To the mixture was added at 0°C 1N hydrochloric acid (200ml), and the mixture was stirred at 30 minutes and extracted with ethyl acetate (twice). The organic layer was washed with saturated brine (twice) and dried with magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the resulting solid was washed with hexane (35ml) and dried in vacuo to give colorless solid of 3-methyl-4-propoxyphenyl borate (1.32g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.00 (t, 3H, J=7.4 Hz), 1.66-1.83 (m, 2H), 2.14 (s, 3H), 3.94 (t, 2H, J=6.6 Hz), 6.85 (d, 1H, J=8.0 Hz), 7.52-7.61 (m, 2H), 7.75 (s, 2H).  
Reference Example 197

To a suspension of 4-propoxyphenol (10.0g) and potassium carbonate (10.0g) in DMF (50ml) was added bromoacetaldehydedimethylacetal (12.2g), and the mixture was refluxed for 14 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with 1N sodium hydroxide solution (twice) and then washed with saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give yellow oil of 4-(2,2-dimethoxy)ethoxypropoxybenzene (12.2g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.02 (t, 3H, J=7.4 Hz), 1.69-1.83 (m, 2H), 3.45 (s, 6H), 3.86 (t, 2H, J=6.6 Hz), 3.96 (d, 2H, J=5.6 Hz), 4.70 (t, 1H, J=5.2 Hz), 6.78-6.89 (m, 4H).  
Reference Example 198

To a suspension of polyphosphoric acid (5.2g) in toluene (120ml) was added 4-(2,2-dimethoxy)ethoxypropoxybenzene (5.0g), and the mixture was stirred at 100°C overnight and cooled. To the mixture was added water, and

the mixture was separated. The organic layer was washed with 1N sodium hydroxide solution and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give brown oil of 5-propoxybenzofuran (1.7g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>)  $\delta$  1.05 (t, 3H, J=7.4 Hz), 1.74-1.92 (m, 2H), 3.95 (t, 2H, J=6.6 Hz), 6.69 (dd, 1H, J=2.2, 0.8 Hz), 6.90 (dd, 1H, J=9.2, 2.6 Hz), 7.05 (d, 1H, J=2.6 Hz), 7.37 (d, 1H, J=9.4 Hz), 7.58 (d, 1H, J=2.2 Hz).

#### Reference Example 199

To a solution of 5-propoxybenzofuran (1.50g) in anhydrous tetrahydrofuran (15ml) was added dropwise at 0°C, under argon atmosphere, a solution of n-butyllithium in hexane (1.6M, 6.4ml) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred for 2 hours. To the mixture was added at -78°C a solution of trimethyl borate (2.65g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred overnight while gradually warming to room temperature. At 0°C, to the reaction solution was added 1N hydrochloric acid, and the mixture was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate.

Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give red solid of 5-propoxybenzofuran-2-yl borate (0.62g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$  1.06 (t, 3H, J=7.4 Hz), 1.75-1.92 (m, 2H), 3.95 (t, 2H, J=6.6 Hz), 5.27 (br, 2H), 6.98 (dd, 1H, J=9.2, 3.0 Hz), 7.07 (d, 1H, J=2.6 Hz), 7.30 (d, 1H, J=0.8 Hz), 7.39 (d, 1H, J=8.8 Hz).

#### Reference Example 200

To a suspension of 4-methoxyphenol (26.7g) and potassium carbonate (32.8g) in DMF (150ml) was added bromoacetaldehydedimethylacetal (40.1g), and the mixture was refluxed for 2.5 hours and cooled. To the mixture was

added water, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with 1N sodium hydroxide solution (twice) and then washed with saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give dark brown oil of 4-methoxy-(2,2-dimethoxy)ethoxybenzene (40.4g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.45 (s, 6H), 3.77 (s, 3H), 3.96 (d, 2H, J=5.2 Hz), 4.70 (t, 1H, J=5.2 Hz), 6.79-6.90 (m, 4H).

10 Reference Example 201

To a suspension of polyphosphoric acid (38.3g) in toluene (400ml) was added 4-methoxy-(2,2-dimethoxy)ethoxybenzene (38.0g), and the mixture was stirred at 100°C overnight and cooled. To the mixture was added water, and the mixture was separated. The organic layer was washed with 1N sodium hydroxide solution and then washed with saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give brown oil of 5-methoxybenzofuran (6.5g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.85 (s, 3H), 6.71-7.00 (m, 2H), 7.06 (d, 1H, J=2.2 Hz), 7.39 (d, 1H, J=9.8 Hz), 7.59 (d, 1H, J=2.2 Hz).

25 Reference Example 202

To a solution of 5-methoxybenzofuran (3.6g) in collidine (20ml) was added lithium iodide (6.5g), and the mixture was refluxed, under argon atmosphere, overnight, cooled, made acidic (pH=4) with hydrochloric acid and extracted with ethyl acetate (thrice). The organic layer was washed with 1N hydrochloric acid (twice) and then washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give yellow oil of 5-hydroxybenzofuran (1.6g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 6.61 (dd, 1H, J=2.2, 0.6 Hz), 6.82 (dd, 1H, J=8.8, 2.6 Hz), 7.01 (d, 1H, J=2.6 Hz), 7.34 (d, 1H, J=8.8 Hz), 7.58 (d, 1H, J=2.2 Hz).

Reference Example 203

5 To a solution of 5-hydroxybenzofuran (1.90g) in DMF (30ml) were added potassium carbonate (5.09g) and sodium iodide (5.52g) and then was added 2-chloroethylpropylether (3.47g), and the mixture was stirred, under nitrogen atmosphere, at 95°C for 3 days and cooled. To the mixture  
10 was added water, and the mixture was extracted with ethyl acetate (twice). The organic layer washed with 1N sodium hydroxide solution, water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with  
15 silica gel column chromatography to give yellow oil of 5-propoxyethoxybenzofuran (1.22g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J=7.8 Hz), 1.56-1.74 (m, 2H), 3.51 (t, 2H, J=6.4 Hz), 3.81 (t, 2H, J=5.2 Hz), 4.16 (t, 2H, J=4.6 Hz), 6.70 (dd, 1H, J=2.2, 1.2 Hz), 6.94 (dd,  
20 1H, J=9.0, 2.6 Hz), 7.09 (d, 1H, J=2.2 Hz), 7.38 (d, 1H, J=8.8 Hz), 7.59 (d, 1H, J=2.2 Hz).

Reference Example 204

To a solution of 5-propoxyethoxybenzofuran (1.20g) in anhydrous tetrahydrofuran (10ml) was added dropwise at 0°C,  
25 under argon atmosphere, a solution of n-butyllithium in hexane (1.6M, 4.5ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise at -78°C a solution of trimethyl borate (1.54g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred overnight while  
30 gradually warming to room temperature. At 0°C, to the reaction solution was added 1N hydrochloric acid, and the mixture was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under  
35 reduced pressure, the solvent was evaporated, the resulting solid was washed with hexane to give pale red solid of

5-propoxyethoxybenzofuran-2-yl borate (0.82g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (t, 3H, J=7.4 Hz),  
1.45-1.59 (m, 2H), 3.44 (t, 2H, J=6.6 Hz), 3.71 (t, 2H, J=4.4  
Hz), 4.11 (t, 2H, J=4.4 Hz), 6.94 (dd, 1H, J=9.2, 2.6 Hz),  
5 7.19 (d, 1H, J=2.4 Hz), 7.38 (s, 1H), 7.45 (d, 1H, J=9.2  
Hz), 8.51 (s, 2H).

Reference Example 205

To a suspension of 2-hydroxy-4-methoxybenzaldehyde  
(20.0g) and potassium carbonate (20.0g) in 2-butanone (80ml)  
10 was added diethyl bromomalonate (39.3g), and the mixture  
was refluxed under nitrogen atmosphere for 7 hours and cooled.

To the mixture was added water, and the mixture was made  
acidic with 1N hydrochloric acid and extracted with ethyl  
acetate. The organic layer was washed with saturated brine  
15 and dried with magnesium sulfate. Under reduced pressure,  
the solvent was evaporated, and the resulting dark brown  
oil was suspended in a solution of potassium hydroxide  
(20.0g) in ethanol (200ml). The suspension was refluxed for  
1 hour and cooled, and to the mixture was added water. The  
20 mixture was made acidic with 1N hydrochloric acid and  
extracted with ethyl acetate (twice). The organic layer was  
washed with water and saturated brine, and dried with  
magnesium sulfate. Under reduced pressure, the solvent was  
evaporated, and the resulting solid was washed with hexane  
25 to give yellow solid of 6-methoxybenzofuran-2-carboxylic  
acid (11.8g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.89 (s, 3H), 6.91-7.00 (m, 1H),  
7.07 (br, 1H), 7.47-7.62 (m, 2H).

Reference Example 206

30 A suspension of 6-methoxybenzofuran-2-carboxylic acid  
(22.2g) and copper powder (3.7g) in quinoline (200ml) was  
refluxed under nitrogen atmosphere for 2 hours and cooled,  
and to the suspension was added 2N hydrochloric acid. The  
mixture was extracted with ethyl acetate, and the organic  
35 layer was washed with 2N hydrochloric acid (6 times) and  
then washed with water and saturated brine, and dried with

magnesium sulfate. Under reduced pressure, the solvent was evaporated to give dark brown oil of 6-methoxybenzofuran (17.1g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 3.86 (s, 3H), 6.69 (dd, 1H, J=2.2, 1.2 Hz), 6.88 (dd, 1H, J=8.4, 2.2 Hz), 7.04 (br, 1H), 7.45 (d, 1H, J=6.6 Hz), 7.53 (d, 1H, J=1.4 Hz).

Reference Example 207

To a solution of 6-methoxybenzofuran (16.9g) in collidine (200ml) was added lithium iodide (30.5g), and the mixture was refluxed under argon atmosphere for 1 day and cooled. To the mixture was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with 2N hydrochloric acid (5 times) and then washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give dark brown oil of 6-hydroxybenzofuran (2.9g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 5.04 (s, 1H), 6.69 (dd, 1H, J=2.6, 1.0 Hz), 6.79 (dd, 1H, J=8.4, 2.2 Hz), 7.00 (d, 1H, J=2.0 Hz), 7.42 (d, 1H, J=8.4 Hz), 7.52 (d, 1H, J=2.2 Hz).

Reference Example 208

To a solution of 6-hydroxybenzofuran (1.30g) in DMF (15ml) was added potassium carbonate (1.88g) and then was added dropwise bromopropane (1.44g) under nitrogen atmosphere, and the mixture was refluxed overnight. To the mixture was added water, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with water (thrice) and then washed with saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow oil of 7-propoxybenzofuran (0.93g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.06 (t, 3H, J=7.4 Hz), 1.75-1.93 (m, 2H), 3.96 (t, 2H, J=6.6 Hz), 6.69 (d, 1H, J=2.2 Hz), 6.88 (dd, 1H, J=8.4, 2.0 Hz), 7.03 (d, 1H, J=2.2 Hz), 7.44 (d, 1H, J=8.8 Hz), 7.52 (d, 1H, J=2.2 Hz).



## Reference Example 209

To a solution of 6-propoxybenzofuran (0.83g) in anhydrous tetrahydrofuran (12ml) was added dropwise at 0°C, under argon atmosphere, a solution of n-butyllithium in  
5 hexane (1.6M, 4.7ml), and the mixture was stirred for 1 hour.

To the mixture was added dropwise at -78°C a solution of trimethyl borate (1.47g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred overnight while gradually warming to room temperature. At 0°C, to the  
10 reaction solution was added 1N hydrochloric acid, and the mixture was stirred for 30 minutes and extracted with ethyl acetate (twice). The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the  
15 resulting solid was washed with hexane to give pale red solid of 6-propoxybenzofuran-2-yl borate (0.56g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 1.00 (t, 3H, J=7.8 Hz), 1.71-1.81 (m, 2H), 3.97 (t, 2H, J=6.6 Hz), 6.85 (dt, 1H, J=8.4, 2.2 Hz), 7.10 (s, 1H), 7.37 (s, 1H), 7.53 (d, 1H, J=8.4 Hz), 8.41 (s, 2H).

## Reference Example 210

To a solution of 6-hydroxybenzofuran (1.38g) in DMF (40ml) were added potassium carbonate (3.70g) and sodium iodide (4.01g) and then was added 2-chloroethylpropylether  
25 (2.52g), and the mixture was stirred, under nitrogen atmosphere, at 95°C for 3 days and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with 1N sodium hydroxide solution (4 times), water (thrice) and  
30 saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow oil of 6-propoxyethoxybenzofuran (1.50g).

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J=7.4 Hz), 1.56-1.74 (m, 2H), 3.51 (t, 2H, J=6.6 Hz), 3.81 (t, 2H, J=4.4 Hz),  
35 4.17 (t, 2H, J=4.4 Hz), 6.69 (d, 1H, J=2.2 Hz), 6.91 (dd, 1H, J=8.6, 2.2 Hz), 7.06 (d, 1H, J=2.2 Hz), 7.44 (d, 1H,

J=8.6 Hz), 7.53 (d, 1H, J=2.2 Hz).

Reference Example 211

To a solution of 6-propoxyethoxybenzofuran (1.34g) in anhydrous tetrahydrofuran (15ml) was added dropwise at 0°C, under argon atmosphere, a solution of n-butyllithium in hexane (1.6M, 5.7ml), and the mixture was stirred for 1 hour.

To the mixture was added dropwise at -78°C a solution of trimethyl borate (1.90g) in anhydrous tetrahydrofuran (15ml), and the mixture was stirred overnight while gradually warming to room temperature. At 0°C, to the reaction solution was added 1N hydrochloric acid, and the mixture was stirred for 30 minutes and extracted with ethyl acetate (twice). The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give brown solid of 6-propoxyethoxybenzofuran-2-yl borate (0.27g).

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.88 (t, 3H, J=7.0 Hz), 1.45-1.59 (m, 2H), 3.43 (t, 2H, J=6.6 Hz), 3.70 (t, 2H, J=4.6 Hz), 4.17 (t, 2H, J=5.2 Hz), 6.82 (d, 1H, J=2.2 Hz), 6.98 (d, 1H, J=8.8 Hz), 7.55 (d, 1H, J=8.2 Hz), 7.83 (d, 1H, J=2.2 Hz), 8.04 (s, 2H).

Reference Example 212

To a suspension of o-vanillin (25.0g) and potassium carbonate (28.4g) in 2-butanone (100ml) was added diethyl bromomalonate (49.1g), and the mixture was refluxed under nitrogen atmosphere for 7 hours and cooled. To the mixture was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the resulting red oil was suspended in a solution of potassium hydroxide (17.5g) in ethanol (175ml). The suspension was refluxed for 2 hours and cooled, and to the mixture was added water. The mixture was made acidic with 1N hydrochloric

acid and extracted with ethyl acetate (twice). The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give yellow solid of 7-methoxybenzofuran-2-carboxylic acid (11.8g).

5 <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 3.96 (s, 3H), 7.09 (dd, 1H, J=7.4, 1.4 Hz), 7.26 (t, 1H, J=7.8 Hz), 7.33 (dd, 1H, J=6.2, 1.8 Hz), 7.64 (s, 1H).

Reference Example 213

10 A suspension of 7-methoxybenzofuran-2-carboxylic acid (11.04g) and copper powder (1.83g) in quinoline (200ml) was refluxed under nitrogen atmosphere for 2 hours and cooled, and to the suspension was added 2N hydrochloric acid. The mixture was extracted with ethyl acetate, and the organic

15 layer was washed with 2N hydrochloric acid (8 times), water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give dark brown oil of 7-methoxybenzofuran (8.19g).

20 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 4.02 (s, 3H), 6.77 (d, 1H, J=1.8 Hz), 6.81 (dd, 1H, J=6.8, 2.2 Hz), 7.16 (t, 1H, J=7.8 Hz), 7.21 (d, 1H, J=5.6 Hz), 7.63 (d, 1H, J=2.2 Hz).

Reference Example 214

25 To a solution of 7-methoxybenzofuran (8.0g) in collidine (80ml) was added lithium iodide (14.5g), and the mixture was refluxed under argon atmosphere for 1 day and cooled. To the mixture was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with 1N hydrochloric acid (twice),

30 water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give dark brown oil of 7-hydroxybenzofuran (7.0g).

35 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 5.45 (br, 1H), 6.78 (d, 1H, J=2.2 Hz), 6.84 (dd, 1H, J=7.0, 1.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 7.17 (dd, 1H, J=7.8, 1.8 Hz), 7.61 (d, 1H, J=2.2 Hz).

## Reference Example 215

To a solution of 7-hydroxybenzofuran (2.60g) in DMF (30ml) was added potassium carbonate (3.75g) and then was added dropwise bromopropane (2.87g) under nitrogen atmosphere, and the mixture was stirred overnight. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water (thrice) and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated to give brown oil of 7-propoxybenzofuran (2.73g).

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.09 (t, 3H,  $J=7.6$  Hz), 1.84-2.01 (m, 2H), 4.15 (t, 2H,  $J=7.0$  Hz), 6.76 (d, 1H,  $J=2.2$  Hz), 6.80 (dd, 1H,  $J=7.0, 1.8$  Hz), 7.09-7.21 (m, 2H), 7.62 (d, 1H,  $J=2.2$  Hz).

## Reference Example 216

To a solution of 7-propoxybenzofuran (2.4g) in anhydrous tetrahydrofuran (20ml) was added dropwise at  $0^\circ\text{C}$ , under argon atmosphere, a solution of *n*-butyllithium in hexane (1.6M, 15.4ml), and the mixture was stirred for 1 hour. To the mixture was added dropwise at  $-78^\circ\text{C}$  a solution of trimethyl borate (5.0g) in anhydrous tetrahydrofuran (30ml), and the mixture was stirred overnight while gradually warming to room temperature. At  $0^\circ\text{C}$ , to the reaction solution was added 1N hydrochloric acid, and the mixture was stirred for 30 minutes and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was washed with hexane to give pale red solid of 7-propoxybenzofuran-2-yl borate (1.5g).

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (t, 3H,  $J=7.4$  Hz), 1.85-2.02 (m, 2H), 4.15 (t, 2H,  $J=6.6$  Hz), 5.23 (br, 2H), 6.85 (dd, 1H,  $J=7.8, 1.6$  Hz), 7.15 (t, 1H,  $J=7.8$  Hz), 7.22 (dd, 1H,  $J=8.0, 1.2$  Hz), 7.37(s, 1H).

## Reference Example 217

To a solution of 7-hydroxybenzofuran (2.60g) in DMF (70ml) were added potassium carbonate (6.97g) and sodium iodide (7.55g) and then was added 2-chloroethylpropylether (4.76g), and the mixture was stirred, under nitrogen atmosphere, at 95°C for 3 days and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water (thrice) and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give brown oil of 7-propoxyethoxybenzofuran (3.76g).  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J=7.6 Hz), 1.55-1.73 (m, 2H), 3.53 (t, 2H, J=6.6 Hz), 3.88 (t, 2H, J=4.8 Hz), 4.37 (t, 2H, J=5.2 Hz), 6.76 (d, 1H, J=2.0 Hz), 6.84 (dd, 1H, J=7.4, 1.4 Hz), 7.13 (t, 1H, J=6.6 Hz), 7.21 (dd, 1H, J=7.6, 1.6 Hz), 7.62 (d, 1H, J=2.2 Hz).

#### Reference Example 218

To a solution of 7-propoxyethoxybenzofuran (3.4g) in anhydrous tetrahydrofuran (30ml) was added dropwise at 0°C, under argon atmosphere, a solution of n-butyllithium in hexane (1.6M, 14.5ml), and the mixture was stirred for 30 minutes. To the mixture was added dropwise at -78°C a solution of trimethyl borate (4.8g) in anhydrous tetrahydrofuran (30ml), and the mixture was stirred overnight while gradually warming to room temperature. At 0°C, to the reaction solution was added 1N hydrochloric acid, and the mixture was stirred for 30 minutes and extracted with ethyl acetate (twice). The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give brown oil of 7-propoxyethoxybenzofuran-2-yl borate (0.8g).  
<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.87 (t, 3H, J=7.4 Hz), 1.45-1.62 (m, 2H), 3.44 (t, 2H, J=6.6 Hz), 3.78 (t, 2H, J=4.4 Hz), 4.29 (t, 2H, J=4.8 Hz), 6.93 (d, 1H, J=6.6 Hz), 7.11

(t, 1H, J=7.6 Hz), 7.23 (d, 1H, J=7.6 Hz), 7.43 (s, 1H), 8.53 (s, 2H).

Working Example 140 (Production of Compound 137)

In toluene (23ml), ethanol (2.3ml) and water (2.3ml)  
5 were suspended 3-methyl-4-propoxyphenyl borate (219mg),  
7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (450mg) and potassium  
carbonate (312mg), and the suspension was stirred under  
10 argon atmosphere for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (70mg), and the  
mixture was stirred, under argon atmosphere, at 100°C for  
8 hours and cooled. To the mixture was added water, and the  
mixture was extracted with ethyl acetate (twice). The  
15 organic layer was washed with saturated brine and dried with  
magnesium sulfate. Under reduced pressure, the solvent was  
evaporated, and the residue was purified with silica gel  
column chromatography and recrystallized from ethanol  
(125ml) to give colorless crystals of 7-(3-methyl-4-  
20 propoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-  
benzothiepine-4-carboxamide (Compound 137) (242mg).

m.p. 230.5-231.5 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.08 (t, 3H, J=7.4 Hz), 1.70-1.92  
25 (m, 6H), 2.21 (s, 3H), 2.30 (s, 3H), 2.64 (br, 1H), 3.16  
(t, 2H, J=7.2 Hz), 3.38 (dt, 2H, J=8.6, 1.8 Hz), 3.58 (s,  
2H), 3.73 (t, 2H, J=7.2 Hz), 3.96-4.07 (m, 4H), 6.91 (d,  
1H, J=9.2 Hz), 7.30-7.39 (m, 5H), 7.55 (d, 2H, J=8.0 Hz),  
7.63 (s, 1H), 7.67 (d, 1H, J=8.0 Hz), 7.93 (s, 1H), 8.18  
30 (d, 1H, J=8.0 Hz).

Elemental Analysis for C<sub>34</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 69.36 ; H, 6.85 ; N, 4.76 ;

Found. C, 69.13 ; H, 6.78 ; N, 4.64.

Working Example 141 (Production of Compound 138)

35 In toluene (15ml), ethanol (1.5ml) and water (1.5ml)  
were suspended benzofuran-2-yl borate (122mg), 7-bromo-

N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 8 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography and recrystallized from ethanol (120ml) to give colorless crystals of 7-(benzofuran-2-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 138) (188mg). m.p. 234.0-235.0 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.75 (br, 4H), 2.22 (s, 3H), 2.66 (br, 1H), 3.18 (t, 2H, J=6.6 Hz), 3.39 (t, 2H, J=8.6 Hz), 3.59 (s, 2H), 3.74 (t, 2H, J=5.8 Hz), 4.47 (d, 2H, J= 8.8 Hz), 7.21 (s, 1H), 7.28-7.41 (m, 5H), 7.54-7.66 (m, 4H), 7.92-7.96 (m, 3H), 8.23 (d, 1H, J=8.8 Hz).

Working Example 142 (Production of Compound 139)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 5-propoxy-benzofuran-2-yl borate (165mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 8 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium

- sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography and recrystallized from ethanol (750ml) to give colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-7-(5-propoxybenzofuran-2-yl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 139) (115mg).  
m.p. 241.0-242.0 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.07 (t, 3H, J=7.2 Hz), 1.67-1.90 (m, 6H), 2.21 (s, 3H), 2.67 (br, 1H), 3.18 (t, 2H, J=7.4 Hz), 3.38 (dd, 2H, J=10.6, 2.6 Hz), 3.58 (s, 2H), 3.73 (t, 2H, J=7.0 Hz), 3.97 (t, 2H, J=7.0 Hz), 4.04 (d, 2H, J=12.8 Hz), 6.98 (dd, 1H, J=8.6, 2.6 Hz), 7.06-7.13 (m, 2H), 7.32-7.60 (m, 3H), 7.42 (d, 1H, J=8.6 Hz), 7.56 (d, 2H, J=8.8 Hz), 7.89-7.94 (m, 3H), 8.22 (d, 1H, J=8.4 Hz).  
Elemental Analysis for C<sub>35</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>S  
Calcd. C, 68.38 ; H, 6.23 ; N, 4.56 ;  
Found. C, 68.02 ; H, 6.26 ; N, 4.56.
- Working Example 143 (Production of Compound 140)
- In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 5-propoxyethoxy-benzofuran-2-yl borate (198mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 8 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography and recrystallized from ethanol to give colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-7-



(5-propoxyethoxybenzofuran-2-yl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 140) (200mg).

m.p. 227.0-228.0 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (t, 3H, J=7.2 Hz), 1.58-1.80  
5 (m, 6H), 2.22 (s, 3H), 2.65 (br, 1H), 3.18 (t, 2H, J=6.8 Hz), 3.39 (dd, 2H, J=10.6, 2.6 Hz), 3.52 (t, 2H, J=6.6 Hz), 3.58 (s, 2H), 3.73 (t, 2H, J=6.8 Hz), 3.82 (t, 2H, J=5.6 Hz), 4.04 (d, 2H, J=10.8 Hz), 4.18 (t, 2H, J=4.8 Hz), 7.01 (dd, 1H, J=9.2, 2.6 Hz), 7.11 (d, 2H, J=7.4 Hz), 7.32-7.36  
10 (m, 3H), 7.42 (d, 1H, J=9.2 Hz), 7.56 (d, 2H, J=8.4 Hz), 7.90-7.94 (m, 3H), 8.22 (d, 1H, J=8.4 Hz).

Elemental Analysis for C<sub>37</sub>H<sub>42</sub>N<sub>2</sub>O<sub>7</sub>S

Calcd. C, 67.45 ; H, 6.43 ; N, 4.25 :

Found. C, 67.14 ; H, 6.35 ; N, 4.25.

15 Working Example 144 (Production of Compound 141)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 6-propoxy-benzofuran-2-yl borate (165mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for  
20 10 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel  
30 column chromatography and recrystallized from ethanol (40ml) to give colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-7-(6-propoxybenzofuran-2-yl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 141) (192mg).

35 m.p. 215.0-216.0 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.08 (t, 3H, J=7.8 Hz), 1.72-1.77

(m, 4H), 1.81-1.92 (m, 2H), 2.21 (s, 3H), 2.65 (br, 1H), 3.16 (t, 2H, J=6.2 Hz), 3.38 (dt, 2H, J=10.8, 2.4 Hz), 3.58 (s, 2H), 3.73 (t, 2H, J=7.2 Hz), 3.96-4.07 (m, 4H), 6.92 (dd, 1H, J=8.8, 2.2 Hz), 7.04 (s, 1H), 7.11 (s, 1H), 7.31-7.35 (m, 3H), 7.48 (d, 1H, J=8.4 Hz), 7.58 (d, 2H, J=8.6 Hz), 7.83-7.86 (m, 2H), 8.18 (d, 1H, J=8.8 Hz), 8.25 (s, 1H).

Elemental Analysis for  $C_{35}H_{38}N_2O_6S$

Calcd. C, 68.38 ; H, 6.23 ; N, 4.56 ;

Found. C, 68.17 ; H, 6.38 ; N, 4.50.

10 Working Example 145 (Production of Compound 142)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 6-propoxyethoxy-benzofuran-2-yl borate (250mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (262mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 1 day and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography to give yellow amorphous of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-7-(6-propoxyethoxybenzofuran-2-yl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 142) (200mg).

30  $^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  0.86 (t, 3H, J=7.2 Hz), 1.51-1.80 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 3.20 (t, 2H, J=6.6 Hz), 3.31-3.44 (m, 4H), 3.58 (s, 2H), 3.68-3.78 (m, 4H), 4.03 (d, 2H, J=11.4 Hz), 4.19 (t, 2H, J=4.8 Hz), 6.77 (d, 1H, J=2.2 Hz), 7.04 (d, 1H, J=8.4 Hz), 7.30-7.34 (m, 3H), 7.52-7.57 (m, 4H), 7.92-7.98 (m, 3H), 8.24 (d, 1H, J=8.0 Hz).

Elemental Analysis for  $C_{37}H_{42}N_2O_7S \cdot 0.4H_2O$

Calcd. C, 66.72 ; H, 6.35 ; N, 4.21 ;

Found. C, 66.42 ; H, 6.49 ; N, 4.01.

Working Example 146 (Production of Compound 143)

- 5 In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 7-propoxy-benzofuran-2-yl borate (165mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (208mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 8 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography and recrystallized from ethanol to give colorless crystals of N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-7-(7-propoxybenzofuran-2-yl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 143) (213mg).
- 20 m.p. 246.5-247.5 °C
- 25  $^1H$ -NMR (200MHz,  $CDCl_3$ )  $\delta$  1.12 (t, 3H, J=7.4 Hz), 1.76 (br, 4H), 1.90-2.01 (m, 2H), 2.21 (s, 3H), 2.65 (br, 1H), 3.17 (t, 2H, J=7.8 Hz), 3.38 (dt, 2H, J=11.8, 3.4 Hz), 3.58 (s, 2H), 3.74 (t, 2H, J=7.2 Hz), 4.05 (d, 2H, J=11.0 Hz), 4.19 (t, 2H, J=6.6 Hz), 6.87 (dd, 1H, J=6.6, 2.6 Hz), 7.14-7.24 (m, 3H), 7.32-7.55 (m, 3H), 7.57 (d, 2H, J=8.4 Hz), 7.94-7.99 (m, 3H), 8.22 (d, 1H, J=8.8 Hz).
- 30

Elemental Analysis for  $C_{35}H_{38}N_2O_6S$

Calcd. C, 68.38 ; H, 6.23 ; N, 4.56 ;

Found. C, 68.18 ; H, 6.18 ; N, 4.60.

- 35 Working Example 147 (Production of Compound 144)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml)

were suspended 7-propoxyethoxy-benzofuran-2-yl borate (229mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium carbonate (240mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 8 hours and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography and recrystallized from ethanol (40ml) to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-7-(7-propoxyethoxybenzofuran-2-yl)-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 144) (154mg). m.p. 178.5-179.5 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J=7.8 Hz), 1.56-1.80 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 3.17 (t, 2H, J=6.2 Hz), 3.38 (dt, 2H, J=10.6, 3.0 Hz), 3.54 (t, 2H, J=7.0 Hz), 3.57 (s, 2H), 3.73 (t, 2H, J=7.0 Hz), 3.91 (t, 2H, J=4.6 Hz), 4.03 (d, 2H, J=7.6 Hz), 4.41 (t, 2H, J=5.2 Hz), 6.91 (dt, 1H, J=7.2, 1.8 Hz), 7.13-7.21 (m, 3H), 7.33 (d, 2H, J=8.8 Hz), 7.38 (s, 1H), 7.58 (d, 2H, J=8.4 Hz), 7.91-7.95 (m, 2H), 8.09 (s, 1H), 8.21 (d, 1H, J=8.8 Hz).

Elemental Analysis for C<sub>37</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>S

Calcd. C, 67.45 ; H, 6.43 ; N, 4.25 ;

Found. C, 67.26 ; H, 6.31 ; N, 4.25.

Working Example 148 (Production of Compound 145)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended benzothiophen-2-yl borate (134mg), 7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg) and potassium

carbonate (208mg), and the suspension was stirred under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenyl)phosphinepalladium (47mg), and the mixture was stirred, under argon atmosphere, at 100°C for 1 day and cooled. To the mixture was added water, and the mixture was extracted with ethyl acetate (twice). The organic layer was washed with saturated brine and dried with magnesium sulfate. Under reduced pressure, the solvent was evaporated, and the residue was purified with silica gel column chromatography and recrystallized from ethanol to give colorless crystals of 7-(benzothiophen-2-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 145) (27mg).

m.p. 270.0-271.0 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.75 (br, 4H), 2.21 (s, 3H), 2.65 (br, 1H), 3.18 (t, 2H, J=6.6 Hz), 3.38 (dt, 2H, J=11.8, 3.0 Hz), 3.58 (s, 2H), 3.74 (t, 2H, J=7.4 Hz), 4.05 (d, 2H, J=13.4 Hz), 7.32-7.42 (m, 5H), 7.56 (d, 2H, J=8.2 Hz), 7.69 (s, 1H), 7.76-7.90 (m, 4H), 7.98 (s, 1H), 8.21 (d, 1H, J=8.4 Hz).

Elemental Analysis for C<sub>32</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>·0.1H<sub>2</sub>O

Calcd. C, 66.90 ; H, 5.65 ; N, 4.88 ;

Found. C, 66.67 ; H, 5.60 ; N, 4.91.

Working Example 149 (Production of Compound 146)

To a suspension of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.80g) in ethanol (50ml) was added at room temperature methanesulfonic acid (84 μl), and the mixture was stirred for 1 hour and concentrated under reduced pressure. The residue was crystallized from 2-propanol to give colorless crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide methanesulfonate (Compound

146) (0.78g).

m.p. 178-181 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J=7.5 Hz), 1.56-2.15 (6H, m), 2.59 (3H, s), 2.77 (3H, s), 3.09 (2H, t, J=6.8 Hz),  
5 3.21-3.55 (5H, m), 3.74-3.84 (4H, m), 3.88-4.09 (3H, m),  
4.13-4.32 (3H, m), 7.03 (2H, d, J=8.6 Hz), 7.44 (2H, d, J=8.8 Hz), 7.59-7.67 (3H, m), 7.80-7.92 (4H, m), 8.14 (1H, d, J=8.4 Hz), 9.43 (1H, s), 10.46 (1H, m).

IR (KBr) 3273, 1644, 1607, 1520, 1416, 1318, 1292, 1250,  
10 1246, 1194, 1165 cm<sup>-1</sup>

Elemental Analysis for C<sub>36</sub>H<sub>46</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>·0.25H<sub>2</sub>O

Calcd. C, 60.11 ; H, 6.52 ; N, 3.89 ;

Found. C, 59.93 ; H, 6.48 ; N, 3.85.

Working Example 150 (Production of Compound 147)

15 To a solution of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (1.10g) in THF (40ml) was added at room temperature benzenesulfonic acid (313mg), and the  
20 mixture was stirred for 1 hour and concentrated under reduced pressure. To the residue was added 2-propanol, and the mixture was concentrated under reduced pressure. The residue was crystallized from 2-propanol to give crude crystals, which were recrystallized from 2-propanol to give  
25 colorless crystals of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide benzenesulfonate (Compound 147) (1.19g).

30 m.p. 187-189 °C

<sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>) δ 0.87 (3H, t, J=7.5 Hz), 1.44-1.63 (2H, m), 1.65-1.90 (2H, m), 1.95-2.08 (2H, m), 2.62 (3H, s), 3.02-3.15 (2H, m), 3.25-3.60 (5H, m), 3.69-3.86 (4H, m), 3.94-4.22 (5H, m), 4.47 (1H, d, J=12.0 Hz), 7.10 (2H, d, J=8.8 Hz), 7.29-7.34 (3H, m), 7.49-7.62 (5H, m), 7.74-7.91  
35 (5H, m), 8.05-8.09 (2H, m), 10.39 (1H, s).

IR (KBr) 3239, 1665, 1642, 1605, 1518, 1318, 1292, 1167, 1121, 1017  $\text{cm}^{-1}$

Elemental Analysis for  $\text{C}_{41}\text{H}_{46}\text{N}_2\text{O}_9\text{S}$

Calcd. C, 63.38 ; H, 6.23 ; N, 3.61 :

5 Found. C, 63.14 ; H, 6.20 ; N, 3.72.

Working Example 151 (Production of Compound 148)

To a solution of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (1.10g) in acetone (150ml) was added at room temperature 47% sulfuric acid (0.27ml), and the mixture was stirred for 0.5 hours and concentrated under reduced pressure. To the residue was added 2-propanol, and the mixture was concentrated. To the residue was added 2-propanol, and the resulting solid was collected by filtration and dissolved in 2-propanol under heating. The solution was cooled, and the resulting powder was collected by filtration to give colorless amorphous of N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide sulfate (Compound 148) (1.21g).

$^1\text{H-NMR}$  (200MHz,  $\text{DMSO-d}_6$ )  $\delta$  0.88 (3H, t,  $J=7.5$  Hz), 1.44-1.62 (2H, m), 1.64-2.11 (4H, m), 2.62 (3H, br s), 3.02-3.15 (2H, m), 3.24-3.57 (5H, m), 3.67-3.87 (4H, m), 3.95-4.23 (5H, m), 4.38-4.58 (1H, m), 7.10 (2H, d,  $J=9.2$  Hz), 7.49-7.56 (3H, m), 7.74-7.91 (5H, m), 8.05-8.09 (2H, m), 10.38 (1H, s).

IR (KBr) 3274, 1663, 1606, 1518, 1414, 1292, 1252, 1127  $\text{cm}^{-1}$

30 Elemental Analysis for  $\text{C}_{35}\text{H}_{44}\text{N}_2\text{O}_{10}\text{S}_2 \cdot 0.5\text{H}_2\text{O}$

Calcd. C, 57.91 ; H, 6.25 ; N, 3.86 ;

Found. C, 57.95 ; H, 6.22 ; N, 4.01.

Working Example 152 (Production of Compound 149)

To a solution of 7-(4-butoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (300mg)

- in DMF (7ml) was added at room temperature methyl iodide (63 $\mu$ l), and the mixture was stirred for 18 hours and concentrated under reduced pressure. To the residue was added ethyl acetate, and the resulting crystals were
- 5 collected by filtration and recrystallized from ethanol to give pale yellow of crystals N-[4-[[7-(4-butoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carbonyl]amino]benzyl]-N,N-dimethyltetrahydro-2H-pyran-4-aminium iodide (Compound 149) (290mg).
- 10 m.p. 186-190°C
- <sup>1</sup>H-NMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$  0.95 (3H, t, J=7.3 Hz), 1.36-1.55 (2H, m), 1.66-2.00 (4H, m), 2.09-2.55 (2H, m), 2.88 (6H, s), 3.01-3.16 (2H, m), 3.23-3.66 (3H, m), 3.77-3.84 (2H, m), 4.00-4.15 (4H, m), 4.47 (2H, s), 7.09 (2H, d, J=8.8 Hz),
- 15 7.55-7.59 (3H, m), 7.76 (2H, d, J=8.8 Hz), 7.86-7.91 (3H, m), 8.06-8.10 (2H, m), 10.44 (1H, s).
- IR (KBr) 3220, 1669, 1607, 1593, 1518, 1474, 1410, 1314, 1285, 1246, 1128 cm<sup>-1</sup>
- Elemental Analysis for C<sub>35</sub>H<sub>43</sub>N<sub>2</sub>O<sub>5</sub>SI·0.5H<sub>2</sub>O
- 20 Calcd. C, 56.83 ; H, 6.00 ; N, 3.79 ;
- Found. C, 56.58 ; H, 6.13 ; N, 3.63.
- Reference Example 219
- With using CHIRALCEL OD (hexane/ethano=18:2), (4-aminophenyl)-(2-pyridyl)methanol (0.93g) was separated to
- 25 give (+)-(4-aminophenyl)-(2-pyridyl)methanol (0.41g, 99.6%ee) and (-)-(4-aminophenyl)-(2-pyridyl)methanol (0.43g, 99.4%ee).
- (+)-(4-aminophenyl)-(2-pyridyl)methanol [α]<sub>D</sub> = +43.4°
- (-)-(4-aminophenyl)-(2-pyridyl)methanol [α]<sub>D</sub> = -43.6°
- 30 Working Example 153 (Production of Compound 150)
- To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (300mg) in THF (10ml) were added at room temperature thionyl chloride (0.1ml) and DMF (1 drop), and the mixture was
- 35 stirred 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml).



At 0°C, the solution was added dropwise to a solution of (+)-(4-aminophenyl)-(2-pyridyl)methanol (150mg) and triethylamine (0.58ml) in THF (5ml), and the mixture was stirred at room temperature for 40 hours. To the mixture  
5 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethyl acetate) to give colorless crystals  
10 of 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 150) (273mg).  
m.p. 173-174 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.1 Hz), 1.30-1.46 (2H, m), 1.52-1.66 (2H, m), 3.11-3.18 (2H, m), 3.55 (2H, t, J=6.6 Hz), 3.68-3.75 (2H, m), 3.79-3.84 (2H, m), 4.16-4.20 (2H, m), 5.32 (1H, d, J=4.4 Hz), 5.75 (1H, d, J=4.4 Hz), 7.04 (2H, d, J=8.8 Hz), 7.12-7.28 (2H, m), 7.34 (1H, s), 7.39 (2H, d, J=8.6 Hz), 7.52-7.69 (7H, m), 7.96 (1H, s), 8.19  
20 (1H, d, J=8.4 Hz), 8.56-8.59 (1H, m).

IR (KBr) 3403, 3339, 1649, 1609, 1595, 1518, 1314, 1289, 1252, 1128 cm<sup>-1</sup>

Elemental Analysis for C<sub>35</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S

Calcd. C, 68.61 ; H, 5.92 ; N, 4.57 :

25 Found. C, 68.60 ; H, 5.98 ; N, 4.53.

Working Example 154 (Production of Compound 151)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 150)  
30 (230mg) in dichloromethane (10ml) was added at 0°C 3-chloroperbenzoic acid (70%, 0.12g), and the mixture was stirred at room temperature for 24 hours. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes and extracted with  
35 ethyl acetate. The organic layer was washed with sodium bicarbonate solution and saturated brine, dried with

- magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:9→1:4) to give colorless crystals of 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[hydroxy(1-
- 5 oxidopyridin-2-yl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 151) (187mg).  
m.p. 125-128 °C
- <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.3 Hz), 1.30-1.46 (2H, m), 1.54-1.68 (2H, m), 3.14-3.20 (2H, m), 3.56 (2H, t, J=6.6
- 10 Hz), 3.68-3.75 (2H, m), 3.79-3.84 (2H, m), 4.16-4.21 (2H, m), 6.07 (1H, d, J=4.6 Hz), 6.38 (1H, d, J=4.6 Hz), 6.94-7.01 (1H, m), 7.04 (2H, d, J=9.2 Hz), 7.24-7.28 (1H, m), 7.37 (1H, s), 7.44-7.56 (5H, m), 7.62-7.69 (4H, m), 8.06 (1H, s), 8.18 (1H, d, J=8.0 Hz), 8.24-8.28 (1H, m).
- 15 IR (KBr) 3351, 3118, 1665, 1605, 1518, 1310, 1291, 1252, 1167, 1130 cm<sup>-1</sup>
- Elemental Analysis for C<sub>35</sub>H<sub>36</sub>N<sub>2</sub>O<sub>7</sub>S·1.0H<sub>2</sub>O  
Calcd. C, 65.00 ; H, 5.92 ; N, 4.33 ;  
Found. C, 65.02 ; H, 5.90 ; N, 4.16.
- 20 Working Example 155 (Production of Compound 152)
- To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (300mg) in THF (10ml) were added at room temperature thionyl chloride (0.1ml) and DMF (1 drop), and the mixture was
- 25 stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml).  
At 0°C, the solution was added dropwise a solution of (-)-(4-aminophenyl)-(2-pyridyl)methanol (150mg) and triethylamine (0.58ml) in THF (3ml), and the mixture was
- 30 stirred at room temperature for 64 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the resulting crystals were collected by
- 35 filtration and washed with ethyl acetate to give colorless crystals of 7-[4-(2-butoxyethoxy)phenyl]-N-[4-

[hydroxy(2-pyridyl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 152) (201mg).

m.p. 171-173 °C

5 <sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.1 Hz), 1.30-1.46 (2H, m), 1.52-1.72 (2H, m), 3.11-3.17 (2H, m), 3.56 (2H, t, J=6.8 Hz), 3.68-3.75 (2H, m), 3.79-3.84 (2H, m), 4.16-4.20 (2H, m), 5.34 (1H, br s), 5.75 (1H, br s), 7.03 (2H, d, J=8.8 Hz), 7.12-7.28 (2H, m), 7.33 (1H, s), 7.38 (2H, d, J=8.4 Hz), 7.52-7.69 (7H, m), 8.02 (1H, s), 8.18 (1H, d, J=8.2 Hz), 8.56-8.58 (1H, m).

10 IR (KBr) 3448, 3339, 1649, 1609, 1595, 1518, 1312, 1289, 1252, 1128 cm<sup>-1</sup>

Elemental Analysis for C<sub>35</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S·0.25H<sub>2</sub>O

15 Calcd. C, 68.11 ; H, 5.96 ; N, 4.54 ;

Found. C, 68.09 ; H, 5.84 ; N, 4.50.

Working Example 156 (Production of Compound 153)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 152) (157mg) in dichloromethane (10ml) was added at 0°C 3-chloroperbenzoic acid (70%, 98mg), and the mixture was stirred at room temperature for 2 days. To the reaction mixture was added sodium thiosulfate solution, and the mixture was stirred for a few minutes and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate solution and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:9→1:4) to give pale yellow crystals of 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[hydroxy(1-oxidopyridin-2-yl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 153) (67mg).

35 m.p. 104-107 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J=7.1 Hz), 1.30-1.46 (2H,

m), 1.54-1.68 (2H, m), 3.14-3.20 (2H, m), 3.56 (2H, t, J=6.6 Hz), 3.68-3.75 (2H, m), 3.79-3.84 (2H, m), 4.16-4.21 (2H, m), 6.06 (1H, s), 6.94-7.01 (1H, m), 7.04 (2H, d, J=8.8 Hz), 7.24-7.28 (1H, m), 7.37 (1H, s), 7.44-7.56 (5H, m), 7.62-7.69 (4H, m), 8.13 (1H, s), 8.18 (1H, d, J=8.0 Hz), 8.24-8.28 (1H, m).

IR (KBr) 3368, 3210, 1663, 1607, 1518, 1310, 1292, 1252, 1128  $\text{cm}^{-1}$

Elemental Analysis for  $\text{C}_{35}\text{H}_{36}\text{N}_2\text{O}_7\text{S}\cdot 1.0\text{H}_2\text{O}$

10 Calcd. C, 65.00 ; H, 5.92 ; N, 4.33 ;

Found. C, 65.06 ; H, 5.81 ; N, 4.28.

Working Example 157 (Production of Compound 154)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (200mg) in THF (10ml) were added at room temperature thionyl chloride (0.067ml) and DMF (1 drop), and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15ml):

The solution was added dropwise at 0°C to a solution of 1-(4-aminobenzyl)-phosphorinane-1-oxide (154mg) and triethylamine (0.33ml) in THF/DMF (5/5ml), and the mixture was stirred at room temperature for 20 hours. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate=1:3→1:2) and recrystallized from ethanol/2-propanol to give colorless crystals of 7-[4-(2-butoxyethoxy)phenyl]-N-(4-pentamethylenephosphorylmethylphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 154) (114mg).

m.p. 222-224 °C

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, t, J=7.2 Hz), 1.34-1.76 (12H, m), 1.82-2.11 (2H, m), 3.13 (2H, d, J=13.2 Hz), 3.17-3.23 (2H, m), 3.58 (2H, t, J=6.6 Hz), 3.67-3.74 (2H,

m), 3.80-3.84 (2H, m), 4.16-4.21 (2H, m), 7.04 (2H, d, J=8.4 Hz), 7.21-7.26 (2H, m), 7.46 (1H, s), 7.53-7.69 (6H, m), 8.20 (1H, d, J=8.0 Hz), 8.76-8.90 (1H, m).

IR (KBr) 3185, 1661, 1597, 1516, 1252, 1159, 1130  $\text{cm}^{-1}$

5 Elemental Analysis for  $\text{C}_{35}\text{H}_{42}\text{NO}_6\text{SP}$

Calcd. C, 66.12 ; H, 6.66 ; N, 2.20 ;

Found. C, 65.81 ; H, 6.58 ; N, 2.38.

Reference Example 220

In acetone (100ml) were suspended 4-bromo-1,2-dihydroxybenzene (9.0g), 1-bromopropane (9.1ml), potassium carbonate (19.7g) and sodium iodide (15.0g), and the mixture was refluxed overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with distillation under reduced pressure to give 4-bromo-1,2-dipropoxybenzene (11.2g) as colorless oil.  $\text{bp}_{0.8} = 114-118^\circ\text{C}$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.03 (3H, t, J= 7.3 Hz), 1.04 (3H, t, J= 7.4 Hz), 1.73-1.93 (4H, m), 3.92 (2H, t, J= 6.8 Hz), 3.93 (2H, t, J= 6.6 Hz), 6.74 (1H, d, J= 9.0 Hz), 6.96-7.01 (2H, m).

IR (neat)  $\nu$  2965, 2938, 2878, 1586, 1503, 1470  $\text{cm}^{-1}$ .

25 Reference Example 221

In THF (5ml) was suspended magnesium (1.1g), and to the suspension was added under nitrogen atmosphere dibromoethane (catalytic amount) and then was added dropwise a solution of 4-bromo-1,2-dipropoxybenzene (11.2g) in THF (30ml). The mixture was stirred at  $50^\circ\text{C}$  for 1 hour and cooled with dry ice/acetone, and to the mixture was added dropwise trimethoxyborane (9.2ml). The mixture was stirred at room temperature overnight, and to the mixture was added 1N hydrochloric acid. The mixture was stirred at room temperature for 30 minutes, concentrated and extracted with ethyl acetate. The organic layer was washed with water and

saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 3,4-dipropoxyphenyl borate (7.1g) as colorless crystals.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.95-1.04 (6H, m), 1.63-1.77 (4H, m),  
5 3.87-3.95 (4H, m), 6.90 (1H, d, J= 8.0 Hz), 7.32-7.39 (2H, m), 7.82 (1H, s).

Working Example 158 (Production of Compound 155)

A mixture of 7-bromo-N-(4-((N-methyl-N-(  
(tetrahydro-2H-pyran-4-yl)amino)methyl)phenyl)-1,1-  
10 dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (0.3g),  
3,4-dipropoxyphenyl borate (0.17g), 1M potassium carbonate  
solution (1.3ml), ethanol (1.3ml) and toluene (25ml) was  
stirred under argon atmosphere at room temperature for 30  
minutes. To the mixture was added  
15 tetrakis(triphenylphosphine)palladium (0.03g), and the  
mixture was refluxed under argon atmosphere for 6 hours and  
extracted with ethyl acetate. The organic layer washed with  
water and saturated brine and dried with anhydrous magnesium  
sulfate, and the solvent was evaporated. The residue was  
20 purified with silica gel column chromatography (ethyl  
acetate/methanol/triethylamine) to give crude crystals,  
which were recrystallized from ethanol to give 7-(3,4-  
dipropoxyphenyl)-N-(4-((N-methyl-N-(tetrahydro-2H-  
pyran-4-yl)amino)methyl)phenyl)-1,1-dioxo-2,3-dihydro-  
25 1-benzothiepine-4-carboxamide (Compound 155) (0.27g) as  
colorless crystals.

mp 206-208 °C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.07 (6H, t, J= 7.5 Hz), 1.63-1.97 (8H, m),  
2.21 (3H, s), 2.59-2.67 (1H, m), 3.17 (2H, t, J= 6.7 Hz),  
30 3.38(2H, dt, J= 3.2, 22.0 Hz), 3.58 (2H, s), 3.71 (2H, t,  
J= 6.7 Hz), 3.99-4.08 (6H, m), 6.97 (1H, d, J= 8.2 Hz),  
7.11-7.17 (2H, m), 7.31-7.35 (3H, m), 7.53-7.66 (4H, m),  
7.85 (1H, s), 8.18 (1H, d, J=8.2 Hz).

IR (KBr) ν 3330, 2963, 1667, 1597, 1520 cm<sup>-1</sup>.

35 Anal. calcd. for C<sub>36</sub>H<sub>44</sub>N<sub>2</sub>O<sub>8</sub>S: C, 68.33; H, 7.01; N, 4.43.  
Found C, 68.25; H, 7.06; N, 4.32.

## Working Example 159 (Production of Compound 156)

In DMF (8ml) were dissolved 7-(4-(2-butoxyethoxy)phenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (0.4g), 2-(4-aminobenzyl)-1,3,2-dioxaphosphorinane-2-oxide (0.22g) and 1-hydroxybenzotriazole (0.13g), and to the solution were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.36g) and triethylamine (0.4ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, poured into water and extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give crude crystals, which were recrystallized from ethanol to give 2-(4-(7-(4-(2-butoxyethoxy)phenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylamino) benzyl)-1,3,2-dioxaphosphorinane-2-oxide (Compound 156) (0.40g) as colorless crystals.

mp 222-223 °C.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.93 (3H, t, J= 7.3 Hz), 1.21-1.48 (2H, m), 1.55-1.69 (2H, m), 1.70-1.90 (2H, m), 3.12-3.18 (2H, m), 3.24 (2H, d, J= 21.2 Hz), 3.56 (2H, t, J= 6.6 Hz), 3.69-3.75 (2H, m), 3.82 (2H, t, J= 5.0 Hz), 4.02-4.21 (4H, m), 4.33-4.47 (2H, m), 7.04 (2H, d, J= 8.8 Hz), 7.23-7.28 (1H, m), 7.43 (1H, s), 7.52-7.68 (6H, m), 8.18 (1H, d, J=8.6 Hz), 8.44 (1H, br).

IR (KBr) ν 2957, 2922, 1657, 1607, 1597, 1537, 1518 cm<sup>-1</sup>.

Anal. calcd. for C<sub>33</sub>H<sub>38</sub>NO<sub>8</sub>PS: C, 61.96; H, 5.99; N, 2.19.

Found C, 61.63; H, 6.25; N, 2.07.

## 30 Working Example 160 (Production of Compound 157)

To a solution of 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (205mg) in THF (10ml) were added at room temperature thionyl chloride (0.08ml) and DMF (1 drop), and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15ml). The solution

was added dropwise at 0°C to a solution of (+)-(4-aminophenyl)-(2-pyridyl)methanol (121mg) and triethylamine (0.46ml) in THF (5ml), and the mixture was stirred at room temperature for 40 hours. To the mixture  
5 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with sodium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethyl acetate) to give colorless crystals  
10 of N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 157) (220mg).

m.p. 208-210 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J=7.5 Hz), 1.75-1.92 (2H, m), 3.11-3.18 (2H, m), 3.68-3.75 (2H, m), 3.98 (2H, t, J=6.6 Hz), 5.33 (1H, d, J=4.0 Hz), 5.75 (1H, d, J=4.0 Hz), 7.00 (2H, d, J=8.8 Hz), 7.12-7.28 (2H, m), 7.34 (1H, s), 7.39 (2H, d, J=8.6 Hz), 7.52-7.69 (7H, m), 7.89 (1H, s), 8.19 (1H, d, J=8.0 Hz), 8.54-8.60 (1H, m).

20 Working Example 161 (Production of Compound 158)

To a solution of N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 157) (180mg) in dichloromethane (10ml) was added at 0°C 3-  
25 chloroperbenzoic acid (70%, 96mg), and the mixture was stirred at room temperature for 18 hours. To the reaction mixture was added a solution of sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with ethyl acetate. The organic layer was washed with a solution  
30 of sodium bicarbonate and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate = 1:9→1:4) and crystallized from ethanol/diisopropylether to give colorless crystals of  
35 N-[4-[hydroxy(1-oxidepyridin-2-yl)methyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-



carboxamide (Compound 158) (99mg).

m.p. 184-186 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.07 (3H, t, J=7.6 Hz), 1.76-1.94 (2H, m), 3.14-3.20 (2H, m), 3.69-3.76 (2H, m), 3.99 (2H, t, J=6.6 Hz), 6.07 (1H, d, J=4.4 Hz), 6.40 (1H, d, J=4.4 Hz), 6.94-7.03 (3H, m), 7.24-7.29 (2H, m), 7.38 (1H, s), 7.47 (2H, d, J=8.8 Hz), 7.54 (2H, d, J=9.2 Hz), 7.63-7.70 (4H, m), 8.04 (1H, s), 8.19 (1H, d, J=8.0 Hz), 8.25-8.28 (1H, m).

Working Example 162 (Production of Compound 159)

10 To a solution of 7-(4-butoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxylic acid (240mg) in THF (10ml) were added at room temperature thionyl chloride (0.09ml) and DMF (1 drop), and the mixture was stirred for 1 hour. Under reduced pressure, the solvent was evaporated, 15 and the residue was dissolved in THF (20ml). The solution was added dropwise at 0°C to a solution of (+)-(4-aminophenyl)-(2-pyridyl)methanol (137mg) and triethylamine (0.5ml) in THF (5ml), and the mixture was stirred at room temperature for 20 hours. To the mixture 20 was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried with sodium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethyl acetate) to give colorless crystals 25 of 7-(4-butoxyphenyl)-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 159) (253mg).

m.p. 142-145 °C

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.00 (3H, t, J=7.1 Hz), 1.42-1.64 (2H, m), 1.71-1.89 (2H, m), 3.15 (2H, t, J=6.8 Hz), 3.72 (2H, t, J=6.8 Hz), 4.02 (2H, t, J=6.5 Hz), 5.34 (1H, d, J=3.7 Hz), 5.75 (1H, d, J=3.7 Hz), 7.00 (2H, d, J=8.8 Hz), 7.12-7.29 (2H, m), 7.34 (1H, s), 7.39 (2H, d, J=8.8 Hz), 7.52-7.69 (7H, m), 7.94 (1H, s), 8.18 (1H, d, J=8.0 Hz), 8.55-8.61 (1H, m).

35 Working Example 163 (Production of Compound 160)

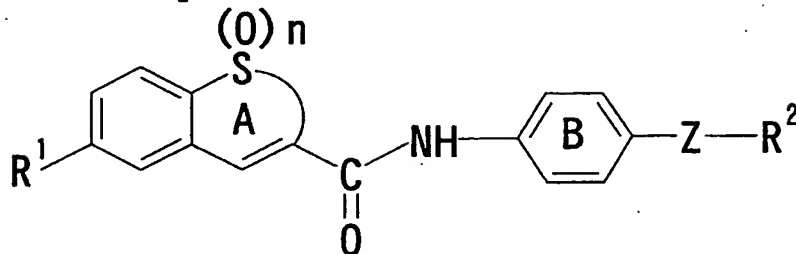
To a solution of 7-(4-butoxyphenyl)-N-[4-[hydroxy(2-pyridyl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 160) (200mg) in dichloromethane (10ml) was added at 0°C 3-chloroperbenzoic acid (70%, 104mg), and the mixture was stirred at room temperature for 20 hours. To the reaction mixture was added a solution of sodium thiosulfate, and the mixture was stirred for a few minutes and extracted with ethyl acetate. The organic layer was washed with a solution of sodium bicarbonate and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure, and the residue was purified with column chromatography (ethanol/ethyl acetate = 1:9→1:4) and crystallized from ethanol/diisopropylether to give pale yellow crystals of 7-(4-butoxyphenyl)-N-[4-[hydroxy(1-oxidepyridin-2-yl)methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide (Compound 163) (125mg).  
m.p. 133-136 °C  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ 1.00 (3H, t, J=7.3 Hz), 1.42-1.65 (2H, m), 1.72-1.86 (2H, m), 3.13-3.20 (2H, m), 3.69-3.75 (2H, m), 4.03 (2H, t, J=6.4 Hz), 6.07 (1H, d, J=4.4 Hz), 6.39 (1H, d, J=4.4 Hz), 6.93-7.05 (3H, m), 7.24-7.29 (2H, m), 7.38 (1H, s), 7.46 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.8 Hz), 7.62-7.69 (4H, m), 8.09 (1H, s), 8.18 (1H, d, J=8.0 Hz), 8.24-8.28 (1H, m).

#### Industrial Applicability

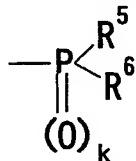
The compound of the formula (I) of the present invention has potent CCR5 antagonistic activity and can be advantageously used for the treatment or prevention of infectious disease of various HIV in human (e.g. AIDS).

## CLAIMS

1. A compound of the formula:



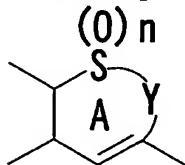
- 5 wherein R¹ is an optionally substituted 5- to 6-membered ring; the ring A is an optionally substituted 6- to 7-membered ring; the ring B is an optionally substituted benzene ring; n is an integer of 1 or 2; Z is a chemical bond or a divalent group; R² is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium, (3) a group binding through a sulfur atom or (4) a group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R⁵ and R⁶ are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R⁵ and R⁶ may bind to each other to form a cyclic group together with the adjacent phosphorus atom, or a salt thereof.
2. A pro-drug of the compound or a salt thereof as claimed in claim 1.
3. A compound according to claim 1, wherein R¹ is benzene,

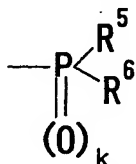
furan, thiophene, pyridine, cyclopentane, cyclohexane, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine or tetrahydropyran, each of which may be substituted.

- 5 4. A compound according to claim 1, wherein R<sup>1</sup> is an optionally substituted benzene.
5. A compound according to claim 1, wherein the ring A is a group of the formula:



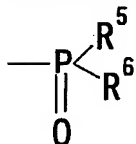
- 10 wherein Y is  $-(CH_2)_m-$  (m is an integer of 1 or 2),  $-CH=CH-$  or  $-N=CH-$ , which may have a substituent at any possible position.
6. A compound according to claim 5, wherein Y is  $-(CH_2)_m-$  (m is an integer of 1 or 2).
- 15 7. A compound according to claim 5, wherein Y is  $-(CH_2)_2-$ .
8. A compound according to claim 1, wherein the ring B is a benzene which may be substituted with a substituent selected from the class consisting of a halogen atom, a C<sub>1-4</sub> alkyl group optionally substituted with a halogen atom and a C<sub>1-4</sub> alkoxy group optionally substituted with a halogen atom.
- 20 9. A compound according to claim 1, wherein n is 2.
10. A compound according to claim 1, wherein Z is an optionally substituted C<sub>1-3</sub> alkylene.
- 25 11. A compound according to claim 1, wherein Z is a divalent group of the formula:  $-Z'-(CH_2)_{n'}-$  (Z' is  $-CH(OH)-$ ,  $-C(O)-$  or  $-CH_2-$ , and n' is an integer of 0-2) in which an optional methylene group may be substituted.
12. A compound according to claim 1, wherein Z is methylene.
- 30 13. A compound according to claim 1, wherein R<sup>2</sup> is (1) an optionally substituted amino group, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring

constituting atoms, (3) a group binding through a sulfur atom or (4) a group of the formula:



wherein k is 0 or 1; and R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group or an optionally substituted amino group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom.

14. A compound according to claim 1, wherein R<sup>2</sup> is (1) an optionally substituted amino group, (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms or (3) a group of the formula:



- 15 wherein R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom.

15. A compound according to claim 1, wherein R<sup>2</sup> is a group of the formula: -NRR'

wherein R and R' are independently an optionally substituted aliphatic hydrocarbon group or an optionally substituted non-aromatic heterocyclic ring group.

16. A compound according to claim 15, wherein R is an optionally substituted acyclic hydrocarbon group and R' is an optionally substituted alicyclic hydrocarbon group or an optionally substituted non-aromatic heterocyclic ring group.

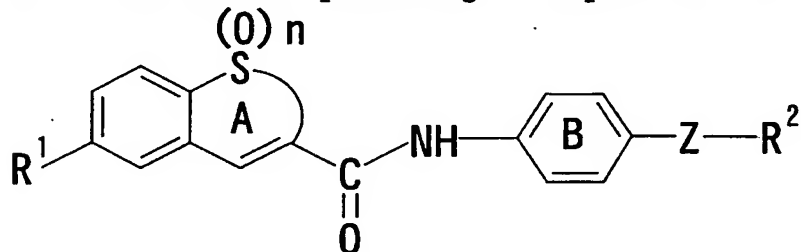
17. A compound according to claim 15, wherein R is an optionally substituted C<sub>1-6</sub> alkyl group and R' is an

optionally substituted C<sub>3-6</sub> cycloalkyl group or an optionally substituted saturated heterocyclic ring group.

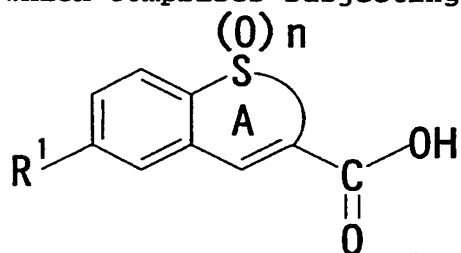
18. A compound according to claim 17, wherein R' is an optionally substituted cyclohexyl, an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted piperidyl.
19. A compound selected from the class consisting of
  - 10 N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-(4-butoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[4-[N-methyl-N-(2-propoxyethyl)amino]phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[4-(2-ethoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[4-(2-ethoxyethoxy)-3,5-dimethylphenyl]-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-[2-chloro-4-(2-propoxyethyl)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide, 7-(3-methyl-4-propoxyphenyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide and 7-(3,4-dipropoxyphenyl)-N-(4-(N-methyl-N-(tetrahydro-2H-
  - 15
  - 20
  - 25
  - 30
  - 35

pyran-4-yl)amino)methyl)phenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepine-4-carboxamide; or a salt thereof.

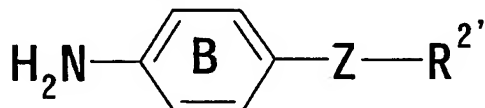
20. A method for producing a compound of the formula:



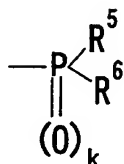
5 each symbol is as defined in claim 1, or a salt thereof, which comprises subjecting a compound of the formula:



10 wherein each symbol is as defined in claim 1, a salt or a reactive derivative thereof to condensation reaction with a compound of the formula:

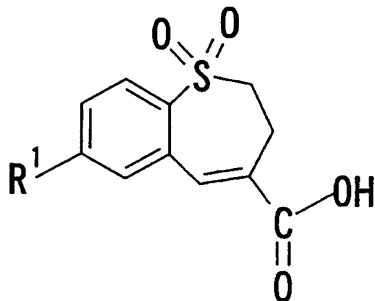


15 wherein B and Z is as defined in claim 1 and R²' is (1) an optionally substituted amino group in which a nitrogen atom may form a quaternary ammonium; (2) an optionally substituted nitrogen-containing heterocyclic ring group which may contain a sulfur atom or an oxygen atom as ring constituting atoms and wherein a nitrogen atom may form a quaternary ammonium; (3) a group binding through a sulfur atom; or (4) a group of the formula:



- wherein k is 0 or 1, and when k is 0, a phosphorus atom may form a phosphonium; and R<sup>5</sup> and R<sup>6</sup> are independently an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted amino group, and R<sup>5</sup> and R<sup>6</sup> may bind to each other to form a cyclic group together with the adjacent phosphorus atom; each of which may be protected, or a salt thereof, and, if desired, subjecting the obtained product to deprotection, oxidation, reduction and/or ammoniation.

21. A compound of the formula:



- wherein R<sup>1</sup> is an optionally substituted 5- to 6-membered ring, or a salt thereof.
22. A pharmaceutical composition which comprises the compound as claimed in claim 1 or a salt thereof.
23. A composition according to claim 22, which is for antagonizing CCR.
24. A composition according to claim 22, which is for antagonizing CCR5.
25. A composition according to claim 22, which is for the treatment or prevention of infectious disease of HIV.
26. A composition according to claim 22, which is for the treatment or prevention of AIDS.
27. A composition according to claim 22, which is for the



prevention of the progression of AIDS.

28. A composition according to claim 25, which is used in combination with a protease inhibitor and/or a reverse transcriptase inhibitor.

5 29. A composition according to claim 28, wherein the reverse transcriptase inhibitor is zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine, delavirdine, efavirenz or abacavir.

10 30. A composition according to claim 28, wherein the protease inhibitor is saquinavir, ritonavir, indinavir, amprenavir or nelfinavir.

31. Use of the compound as claimed in claim 1 or a salt thereof in combination with a protease inhibitor and/or a reverse transcriptase inhibitor for the treatment or

15 prevention of infectious disease of HIV.

32. A method for antagonizing CCR which comprises administering to a mammal in need thereof an effective amount of the compound as claimed in claim 1 or a salt thereof.

20 33. Use of the compound as claimed in claim 1 or a salt thereof, for the manufacture of a medicament for antagonizing CCR.

1/1

## SEQUENCE LISTING

<110> Takeda Chemical Industries, Ltd.  
<120> Anilide Derivative, Production and Use Thereof  
<130> 2582WOOP  
<150> JP 10-363404  
<151> 1998-12-21  
<150> JP 11-170212  
<151> 1999-06-16  
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<213> Artificial Sequence  
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<400> 2  
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International Application No  
PC, JP 99/07148

International Application No  
PC, JP 99/07148

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D337/08 A61K31/38 A61P35/00 A61P31/18

According to international Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category *	Citation of document, with indication, where appropriate, of the relevant passages
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Relevant to claim No.

E WO 00 10965 A (TAKEDA CHEMICAL INDUSTRIES LTD) 2 March 2000 (2000-03-02)  
\* overlap of chemical formulae \*  
the whole document

1-33

P,X WO 99 32100 A (TAKEDA CHEMICAL INDUSTRIES LTD) 1 July 1999 (1999-07-01)  
\* overlap of chemical formulae \*  
the whole document

1-33

P,X WO 99 32468 A (TAKEDA CHEMICAL INDUSTRIES LTD) 1 July 1999 (1999-07-01)  
\* overlap of chemical formulae \*  
the whole document

1-33

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

• Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E' earlier document but published on or after the international filing date

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

**T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*& document member of the same patent family

Date of the actual completion of the international search

3 May 2000

Date of mailing of the international search report

16. 05. 00

Name and mailing address of the ISA  
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Authorized officer

**Stellmach, J**

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 99/07148

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BABA,M. ET AL.: "A small molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV activity " PROC.NATL.ACAD.SCI.USA, vol. 96, May 1999 (1999-05), pages 5698-5703, XP000890061 WASHINGTON * see fig. 1, TAK-779 * the whole document	1-33
A	BALZARINI J ET AL: "INHIBITORY ACTIVITY OF DIARYLAMIDINE DERIVATIVES ON MURINE LEUKEMIA L1210 CELL GROWTH" INVESTIGATIONAL NEW DRUGS,US,MARTINUS NIJHOFF PUBLISHERS, BOSTON, vol. 1, no. 2, 1 January 1983 (1983-01-01), pages 103-114, XP000601220 ISSN: 0167-6997 the whole document	1-33
A	DE CLERCO E ET AL: "DIARYL AMIDINE DERIVATIVES AS ONCORNAVIRAL DNA POLYMERASE INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 23, no. 7, 1 July 1980 (1980-07-01), pages 787-795, XP000573912 ISSN: 0022-2623 the whole document	1-33
A	WO 97 24325 A (TAKEDA CHEMICAL INDUSTRIES LTD ;KATO KANEYOSHI (JP); YAMAMOTO MITS) 10 July 1997 (1997-07-10) the whole document	1-33
A	BRIGHT C ET AL: "Identification of a non peptidic rantes antagonist" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 7, 7 April 1998 (1998-04-07), pages 771-774, XP004136963 ISSN: 0960-894X	1-33
A	G SIMMONS ET AL: "Potent inhibition of HIV-1 infectivity in macrophages and lymphocytes by a novel CCR5 antagonist" SCIENCE,US,AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, vol. 276, 11 April 1997 (1997-04-11), pages 276-279, XP002091209 ISSN: 0036-8075 the whole document	1-33
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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/JP 99/07148

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WELLS T N C ET AL: "Definition, function and pathophysiological significance of chemokine receptors" TRENDS IN PHARMACOLOGICAL SCIENCES,GB,ELSEVIER TRENDS JOURNAL, CAMBRIDGE, vol. 19, no. 9, 1 September 1998 (1998-09-01), pages 376-380, XP004145677 ISSN: 0165-6147	1-33
A,P	HORUK R: "Chemokine receptors and HIV-1: the fusion of two major research fields" IMMUNOLOGY TODAY,GB,ELSEVIER PUBLICATIONS, CAMBRIDGE, vol. 20, no. 2, February 1999 (1999-02), pages 89-94, XP004157282 ISSN: 0167-5699	1-33

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP 99/07148

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 32 IS directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/JP 99/07148

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0010965	A	02-03-2000	WO 9932100 A	01-07-1999
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